UNIVERSIDADE DE LISBOA

Faculdade de Medicina de Lisboa

SOCIAL DISTRESS AND PAIN MODULATION: FINDINGS FROM HEALTHY AND CHRONIC PAIN PATIENTS

Rita Isabel Mangerico Canaipa

Advisor: Alexandre Lemos de Castro Caldas, MD, PhD

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Thesis specially prepared for the degree of Doctor in Biomedical Sciences, Specialty Neuroscience

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The opinions expressed in this publication are the exclusive responsibility of the author.

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To Margarida,

the shiny little flower that blossomed during this work

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This pain

It is a glacier moving through you

And carving out deep valleys

And creating spectacular landscapes

And nourishing the ground

With precious minerals and other stuff

So, don't you become paralyzed with fear

When things seem particularly rough

John Grant in *Glacier, Pale Green Ghosts*,

(The perfect soundtrack for this dissertation)

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LIST OF ABREVIATIONS

ACC = anterior cingulate cortex

AI = anterior insula

BDNF = brain-derived nerve growth factor

CGRP = calcitonin gene-related peptide

CPM = conditioned pain modulation

CVLM = caudal ventrolateral medulla

DLF = dorsolateral funiculus

DLPFC = dorsolateral prefrontal cortex

DMN = default mode network

DNIC = diffuse noxious inhibitory control

EAN = executive attention network

FM = fibromyalgia

fMRI = functional magnetic resonance imaging

GABA = gamma-aminobutyric acid

HC = healthy controls

HPA = hypothalamic-pituitary-adrenal

IASP = International Association for Study of Pain

MVN = medial visual network

NA = nucleus accumbens

NMDA = N-methyl-D-aspartate

NPS = numerical pain scale

OA = osteoarthritis

PAG = periaqueductal gray

PFC = prefrontal cortex

RA = rheumatoid arthritis

RVM = rostral ventromedial medulla

TRP = transient receptor potential

VAS = verbal analogue scale

VPL = ventral posterolateral

ABSTRACT

Pain is a complex experience that integrates sensory, emotional and cognitive dimensions. Understanding how these different dimensions integrate this experience and how each of these dimensions can modulate pain is thus a challenging task. Growing body of evidence showed in the last decades that the central nervous system can increase and decrease the noxious information via the descending pain modulatory system, a conjunction of pro-nociceptive and anti-nociceptive projections tracks that modulate pain. Deficiencies in this system have been proposed has a key element of some chronic pain conditions, mostly in those particularly known to involve central sensitization mechanisms, as Fibromyalgia syndrome.

Among several emotional dimensions that can modulate pain, it has been proposed that social distress threatens well being in a similar mode as pain does, and may share neurocognitive resources and mechanisms with physical pain. In this view it would be expected that social distress would significantly modulate pain experience, but this prediction has not been well established in healthy subjects. Furthermore, this was not, to the best of our knowledge, tested in chronic pain, which is a huge public health problem that, according to the International Association for the Study of Pain, is believed to affect more than 20% of the population worldwide. Based on these theoretical grounds, two studies were developed with the aim of investigating how social distress manipulations modulate pain experience in healthy and chronic pain patients.

In the first study, we aimed to understand the relationship between social distress and pain intensity and unpleasantness in healthy individuals. Sixty participants were enrolled to one condition of a well validated paradigm that induce social distress, the Cyberball game. Electrical stimulation protocol was induced before and after playing the game.

It was found that participants that had a lower electrical unpleasantness threshold were also more distressed by the Cyberball game ($p=0.012$) and that the manipulation itself affected pain intensity ratings ($p=0.001$). The relationship between social distress and physical pain was not related to attachment styles or neuroticism. Overall, this study

provided evidence that sensitivity to social distress is related to sensitivity to physical pain and that social distress modulates pain in healthy individuals.

In the second study, 90 participants were recruited to a study aimed to further investigate how social distress could modulate the pain experience in response to experimental pain models in healthy and two chronic pain conditions: Fibromyalgia, a condition that although recently recognized to have peripheral abnormalities is classically related to central sensitization mechanisms, and Rheumatoid Arthritis, a condition with a well described peripheral inflammation mechanism but less information regarding central sensitization mechanisms. Each participant played the Inclusion and Exclusion condition of Cyberball while pain was induced before and during each condition.

In line with the first study, healthy controls (pain=-13.71±45.28; unplesentness,=-20.78±28.7) and rheumatoid arthritis patients (pain=-7.50±34.54; unplesentness=-5.60±38.04) demonstrated a reduction in pain intensity ratings in response to the electrical induced pain in the Inclusion condition, suggesting the recruitment of the anti-nociceptive projections of the descending pain modulatory system, while in fibromyalgia patients, pain (7.50±26.04, p=0.019) and unplesentness (2.86±31.98, p=0.021) were significantly increased during the same condition. This suggests an impairment of the descending pain modulatory system in fibromyalgia.

These results are discussed in line with evidence of impaired anti-nociceptive projections and changes related to chronic pain that have been found to occur in brain areas as insula, anterior cingulate and midbrain projections, fundamental areas for social connection. Further studies are needed to collect additional information on the nature of the descending pain modulatory system deficits in fibromyalgia. We hope that the increased knowledge regarding the relationships between social events and pain modulation will provide relevant insights for new social and emotional therapeutic approaches in chronic pain conditions, and ultimately contribute to reducing suffering.

Key words:

Pain, Social Distress, Chronic Pain, Fibromyalgia, Descending pain modulatory system

RESUMO

A dor é uma experiência complexa que integra dimensões sensoriais, emocionais e cognitivas. Compreender de que forma estas diferentes dimensões se integram nesta experiência e como é que cada uma delas modula a dor tem-se revelado uma tarefa desafiadora do ponto de vista científico. O crescente desenvolvimento de investigação nas últimas décadas tem demonstrado que essa integração se relaciona com a capacidade do sistema nervoso central inibir ou potenciar o processamento da informação dolorosa através do sistema de modulação descendente da dor.

Este sistema integra áreas como o córtex préfrontal, o córtex do cíngulo anterior e o córtex da ínsula, áreas relacionadas com a componente emocional da dor, em ligação com diversos núcleos do tronco cerebral, sobretudo a substância periaqueductal cinzenta e os núcleos ventromediais rostrais do bolbo raquidiano. Estes núcleos comunicam com a espinhal medula através de projeções serotonergicas, noradrenergicas e dopaminergicas descendentes, aumentando ou diminuindo o processamento de informação. Deste modo, essas projeções tanto poderão ter um efeito inibitório no processamento da dor, isto é, antinociceptivo, como poderão ter um efeito excitatório no processamento da dor, isto é pronociceptivo. Tem sido proposto que deficiências neste sistema modulador descendente poderão ser um aspeto central de algumas síndromes de dor crónica, nomeadamente naquelas que parecem ter um maior envolvimento de mecanismos de sensibilização central, como a Fibromialgia. De facto, diversos estudos têm evidenciado a existência de deficiências no recrutamento de projeções antinociceptivas e um aumento no recrutamento de projeções pronociceptivas nesta síndrome, facto que poderá contribuir significativamente para a dor generalizada reportada por estes doentes.

Diversos investigadores da área das neurociências sociais acreditam que de entre as emoções que podem relacionar-se com a experiência da dor, o sofrimento social que decorre de situações de perda ou ameaça de relações sociais significativas, poderá ter um papel particularmente importante na sua modulação, partilhando com a experiência da dor diversos mecanismos comportamentais e neurocognitivos. De acordo com esta abordagem, as semelhanças entre estas duas experiências resultam do facto de os

humanos, tal como outros mamíferos, serem animais que se desenvolvem em grupos sociais, dependendo não apenas de uma boa condição física mas também de uma boa integração social. Isto poderia, na argumentação dos autores, ter implicado que este sistema social tivesse co-optado os recursos neurocognitivos da dor física, nomeadamente no que diz respeito ao recrutamento das áreas de processamento da componente emocional da dor, como o córtex do cíngulo anterior e a ínsula anterior.

Com base nesta perspetiva, seria de esperar que situações de sofrimento social alterassem significativamente a experiência da dor, mas esta predição tem sido difícil de verificar experimentalmente em indivíduos saudáveis. Acresce ainda que, tanto quanto é do nosso conhecimento, ela nunca foi testada em indivíduos com dor crónica, um importante problema de saúde pública que, de acordo com a *International Association for the Study of Pain* afeta cerca de 20% da população em todo o mundo.

Esta dissertação foi desenvolvida com o objetivo de integrar as duas áreas de conhecimento apresentadas, o estudo da dor e as neurociências sociais, investigando através de dois estudos, de que forma o sofrimento social poderá modular a experiência da dor, em indivíduos saudáveis e em indivíduos com dor crónica.

O primeiro estudo teve como objetivo compreender as relações entre o sofrimento social e, a desagradabilidade e intensidade da dor, em indivíduos saudáveis. Sessenta participantes foram recrutados e sujeitos a uma condição de um paradigma desenvolvido para induzir sofrimento social, o *Cyberball*. O *Cyberball* trata-se de um jogo de computador criado para estudar rejeição social, onde se pretende que o participante passe a bola a outros dois jogadores, que ele pensa serem jogadores “reais” ligados online. Na verdade, o participante está, sem saber, a jogar sozinho com o computador que determina até que ponto será excluído. Neste primeiro estudo, depois de preencherem um conjunto de questionários, os participantes jogaram o *Cyberball*, tendo-lhes sido aplicado um protocolo de estimulação elétrica antes e depois do jogo.

Os resultados mostraram que os indivíduos que apresentavam um limiar de desagradabilidade da dor mais baixo eram os que sentiam mais sofrimento social durante o jogo ($p=0.012$). Em segundo lugar, verificou-se que a manipulação induzida pelo jogo alterava a perceção da intensidade da dor aos estímulos elétricos aplicados depois do

jogo (p=0.001). Foi ainda possível verificar que a relação entre o sofrimento social e a dor física não se relacionava com o estilo de vinculação ou com o neuroticismo, duas dimensões que têm sido teoricamente relacionadas com a sensibilidade ao sofrimento social. Em resumo, este estudo forneceu evidências de que a sensibilidade ao sofrimento social está relacionada com a sensibilidade à dor física, sobretudo nas suas dimensões emocionais, e que o sofrimento social modula significativamente a dor física em indivíduos saudáveis.

No segundo estudo, noventa participantes foram recrutados com o objetivo de compreender de que forma o sofrimento social modula a dor em indivíduos com dor crónica. Nesse sentido, dois modelos experimentais de dor foram investigados em indivíduos saudáveis e em duas condições de dor crónica: na Fibromialgia, síndrome onde têm sido amplamente estudados os mecanismos de sensibilização central, mas onde só recentemente se reconheceu o envolvimento de mecanismos periféricos e na Artrite Reumatóide, onde pelo contrário, os mecanismos inflamatórios periféricos se encontram bem descritos, mas só recentemente se têm reconhecido evidências relacionadas com mecanismos de sensibilização central. Cada participante jogou duas condições do jogo, Inclusão e Exclusão, sendo-lhe induzidos estímulos dolorosos antes e durante cada condição.

Tal como no primeiro estudo, verificou-se que os indivíduos saudáveis (intensidade da dor=-20.78±28.7; desagradabilidade=-13.71±45.28) e com Artrite Reumatóide (intensidade da dor=-7.50±34.54; desagradabilidade=-5.60±38.04) evidenciavam uma redução na intensidade da dor resultante da estimulação elétrica quando participavam na condição de Inclusão do jogo, sugerindo o recrutamento das projeções antinociceptivas do sistema modelador descendente da dor. Pelo contrário, os indivíduos com Fibromialgia revelaram um aumento de dor durante a mesma condição, sugerindo a existência de deficiências no sistema modulador descendente da dor nesta síndrome, que poderão ser particularmente acentuadas em resposta a emoções ou situações sociais positivas (intensidade da dor=7.50±26.04, p=0.019 e desagradabilidade=2.86±31.98, p=0.021).

Estes resultados são discutidos tendo em conta os dados de outros estudos que reportam dificuldades no recrutamento de projeções antinociceptivas na Fibromialgia. Para além disso, estes resultados corroboram também os estudos de neuroimagem que descrevem alterações estruturais e funcionais na dor crónica em áreas como o córtex da ínsula, o córtex da cingulo anterior e as projeções do mesencefalo, áreas que são fundamentais para as motivações e ligações sociais. Alterações nestas áreas poderão ser também centrais nas reorganizações das redes neuronais que se verificam nos processos de transição da dor aguda para os estados de dor crónica.

Os resultados evidenciados pelos estudos aqui descritos destacam a necessidade de desenvolvimento da investigação direcionada à compreensão da natureza das deficiências no sistema modulador descendente da dor na Fibromialgia. Esperamos que o aumento do conhecimento sobre as relações entre as experiências sociais e modulação da dor possam fornecer dados relevantes que se venham a traduzir em novas abordagens terapêuticas sociais e emocionais, para as condições de dor crónica, e com isso contribuir para a redução do sofrimento destes doentes.

Palavras-chave:

Dor, Sofrimento Social, Dor Crónica, Fibromialgia, Sistema Modulador Descendente da Dor

CHAPTERS OUTLINE

The aim of the current dissertation is to study the relationship between social distress and pain experience. Based on this goal, this work was organized into three chapters discussing the relevant body of knowledge that sustained the research developed.

The first chapter summarizes baseline pain concepts and current knowledge about its underlying neuronal processing, from the periphery to its central mechanisms. Evidence regarding the pain modulation and perception in healthy individuals are reviewed and pain assessment methods are presented. The second chapter explores the most relevant studies on pain mechanisms in chronic pain, particularly those related to fibromyalgia (FM), its pathophysiology and its similarities and differences to other painful rheumatic conditions. In the third chapter the theoretical proposals and findings on social neuroscience that are believed to contribute to pain are discussed. Based on previous chapters, the forth chapter presents the scope, aims and hypotheses of the PhD project, which involves two studies. The fifth chapter presents the details of the first study in healthy individuals and the sixth chapter presents the second study in two chronic pain conditions: FM and rheumatoid arthritis (RA). Finally, the seventh chapter discusses the most relevant findings from the two studies and concludes this dissertation.

Chapter 1

1. Pain

The International Association for the Study of Pain defines pain as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey et al., 1994). Pain is a complex and personal experience modulated by sensory and psychological processes. It is a fundamental protection mechanism acting as an alarm system. The study of the relationships between sensory and emotional components of pain, are intriguing and have been matter of intense debate in the last decades is the main goal of the present dissertation.

1.1 Generation of pain

1.1.1 Transduction

Pain is induced by noxious stimulus (mechanical, thermal, electrical and chemical). These stimuli can be found in the external environment, but they can either arise from visceral injuries or even arise in the absence of a stimulus (Derbyshire et al., 2004). The detection of the noxious stimuli depends on the activation of nociceptors, receptors which transform the noxious stimulus into electrical signals, acting as sensory transducers (Sherrington, 1947).

Molecularly, nociceptors are “transient receptor potential” (TRP) channels. TRP channels are a “superfamily” of many different ligand-gated ion channels activated using different molecular mechanisms (receptor activation, ligand activation and direct activation). The detection of a stimulus opens the channel pore and allows an influx of cations (sodium or calcium) triggering action potentials that travel through neuronal pathways to the spinal cord and the higher brain centers.

Some nociceptors are activated by one type of stimulus while others by more than one, thus each nociceptor may differently contribute to diverse pain sensations. Moreover, nociceptors show numerous interactions with other molecules and are able to express many different voltage-gated channels (sodium, potassium or calcium) (Stucky et al., 2009). Overall, this variability allows the transduction of different stimulus parameters: Its quality, location, threshold, intensity and duration. Nociceptors structure and functioning are highly flexible suggesting the significant role that peripheral mechanisms may have in the integration and modulation of pain signals (Ramsey et al., 2006).

Nociceptors are pseudo unipolar: they have their nuclear body at the dorsal root or at trigeminal ganglion (if they provide information from the head and face). One process runs to periphery and the other is directed to the dorsal root ganglion (or the trigeminal ganglion, accordingly).

For pain, there are two important classes of neuron fibers, the A-delta (medium diameter fibers, myelinated, with velocity of conduction about 5 to 30 meters for second) and C-fibers (smaller diameter, unmyelinated fibers, velocity of conduction, about 0.4 to 1.4 meters for second) (Burgess and Perl, 1967; Bessou and Perl, 1969; Djouhri and Lawson, 2004). The A-delta fibers can be mechanosensitives or mechanothermal and induce the earlier pain sensation, the so-called “primary-pain”, and the first rapid, well localized and sharp sensation. Most of the C-fibers are polimodal and can be activated by any modality. They induce the “second-pain”, the delayed and diffuse sensation and represent the most frequent sensory neurons. Other fibers, A-beta nerve fibers which are low threshold thickly myelinated fibers for touch in the somatosensory system, may also contribute to nociception. But this may be a less usual situation.

1.1.2. Transmission

The information from the nociceptor travels through the periphery to the dorsal root ganglion (or trigeminal ganglion, in case of the head and face) and reach the dorsal horn (or brainstem, in the sensory subnucleus caudalis, accordingly), branches and targets

specific segments of spinal cord. In the spinal cord will take place the first synapse, between the nerve fiber and the second order neuron from a cell population called “marginal cells” (Christensen and Perl, 1970).

The synapse between the first and the second neuron involves the release of several neurotransmitters that can be grouped according to its family: non peptidergic (e.g. glutamate) that induce a rapid transmission, or peptidergic (e.g. substance P and calcitonin gene-related peptide, CGRP), involved in slower transmission.

One important step of transmission relates to the branching that occurs in the substantia gelatinosa of the dorsal horn, a local that acts as filter to nociception signals. Here inhibitory and excitatory interneurons modulate the nociception transmission (Todd, 2010). Increases and decreases in the density of some receptors also act as modulators, for example, the endogenous opioids (through the mu- and delta-opiate receptors), GABA (through $GABA_B$ receptors) and endogenous cannabinoids (through CB1 receptors) can dynamically change the transmission in response to inner (e.g., inflammation) or outer conditions (Woolf and Ma, 2007; Kantamneni, 2015).

After the first synapse, the spinal cord projection neurons (second order neurons for pain processing) cross the midline and project rostrally in the contralateral white matter, in the spinothalamic tract, and reach several brainstem areas as caudal ventrolateral medulla, nucleus of the solitary tract, lateral parabrachial area, periaqueductal grey (PAG) and thalamic nuclei (ventral posterolateral nuclei, posterior group, and posterior triangular nucleus). These nuclei are interconnected composing different pain pathways.

Most of the brainstem nuclei are projection targets from dorsal horn second order neurons, as caudal ventrolateral medulla (CVLM) and PAG but they are also strongly involved in descending projection that modulate dorsal horn pain processing. The CVLM and the nucleus of the solitary tract are related to cardio-respiratory reactions to pain (Lima and Almeida, 2002) and connect to rostral ventromedial medulla (RVM), inhibiting its excitatory neurons. Lateral parabrachial area projects to hypothalamus and amygdala (Gauriau and Bernard, 2002) and is related to the emotional and autonomic components of pain experience.

PAG is considered one of the most important subcortical regions implicated in pain processing and modulation. This recognition was first established by Reynolds (1969) who observed that the stimulation of this area in the awaked rat could induce an analgesic reaction. PAG establishes reciprocal projections with several cortical and subcortical pain modulation areas (motor cortex, anterior cingulated cortex, amygdale, and thalamus) and may acts on RVM or directly communicate to the dorsal horn, modulating pain transmission.

Rostral ventromedial medulla receives inputs from PAG and acts on dorsal horn through GABA (γ-aminobutyric acid)-ergic projections. It has a biphasic functioning mode, establishing activation or deactivation connections through the dorsolateral funiculus to dorsal horn with spinal cord. RVM interacts with other important nuclei for pain processing: the nucleus raphe magnus (rich in serotonergic projections), locus coeruleus and other pontine areas (rich in noradrenergic projections) and nucleus reticularis gigantocellularis. These nuclei induce facilitatory and inhibitory connections with dorsal horn as it will be described further. The RVM receives projections for most of cortical pain brain areas, namely, anterior cingulate, insula, and prefrontal cortex. These connections increase under stress situations and have been related to increased arterial pressure and sympathetic activity (Dampney et al., 2002; Gabbott et al., 2005).

Thalamic nuclei are among the most important projection sites for dorsal horn neurons. Many thalamic nuclei receive these inputs, for example, the ventral posterolateral (VPL) nucleus and the posterior triangular nucleus (Gauriau and Bernard, 2004). The first nuclei have reciprocal projections with the primary somatosensory cortex and the later with the secondary somatosensory and insula cortex. Thalamic activations have been related to vigilance, attention, and pain modulation processes, participating in both the sensory and emotional component of pain (Peyron et al., 2000).

The ascending pain signals are further transmitted via a third order neurons projecting from the described nuclei to several forebrain regions. One of these regions is the somatosensory cortex. These activations relates to the sensory components of pain, such as its quality, intensity, and location (Price, 2000). Even though primary and secondary somatosensory cortex may be activated under pain, primary somatosensory

cortex is only activated when the stimulation involves wider body areas or when temporal summation occurs (Staud et al., 2008), being its activations more related to non-nociceptive stimulation (Hu et al., 2015). Another frequently activated region is the Posterior Parietal cortex, which integrate information from different sensory systems and memory processes (Peyron et al, 2000; Price, 2000).

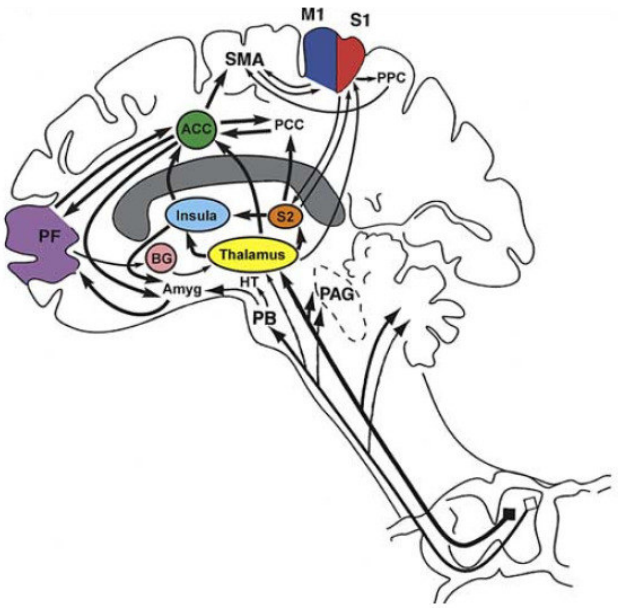
The posterior portion of the insular cortex contributes to the perception of pain intensity (Peyron et al., 2000). In its anterior areas it is related to unset of stimulation (Hu et al., 2015), pain unpleasantness, interoception, introspection and feelings of bodily discomfort (Craig, 2009). It is strongly interconnected with the anterior cingulate cortex (ACC) another key region for the experience of pain that "seems to have a vital and complex role in the interrelation of attentional and evaluative functions with the establishment of emotional valence and response priorities" (Price, pp. 1771, 2000). ACC encodes the affective processing of painful stimuli, its unpleasantness (Rainville et al., 1997), and participates in pain modulation (Tracey and Mantyh, 2007). It is composed of several sub neuroanatomical areas that may be specifically related to different functions (Peyron et al., 2000). As such, the rostral area encodes emotional feelings and is rich in descending projections to brainstem pain modulation regions. ACC is related to placebo analgesia (Bingel et al., 2006) and pain reduction due to distraction and attentional processes (Valet et al., 2004).

Prefrontal cortex has been extensively described has a fundamental region in pain control (for recent reviews see Jeon and Friederici, 2015; Opris and Casanova, 2014). One of its most significant areas is the dorsolateral prefrontal cortex (DLPFC) that relates to attentional processes and emotional control, and has also a key role in pain modulation due to its projections to other cortical and subcortical regions (Lorenz et al., 2003; Wager et al., 2004). It play an important role in placebo analgesia and is usually correlated to low catastrophization and pain control (Seminowicz et al., 2006; Loggia et al., 2015).

The relevance of basal ganglia in pain has been increasingly recognized in the last decade. Basal ganglia are involved in different processes (motor, emotional and cognitive tasks) and it has been considered as a local of “multisensory integration” (Nagy et al., 2006). Concerning pain, this region is an important relay center between cortical and

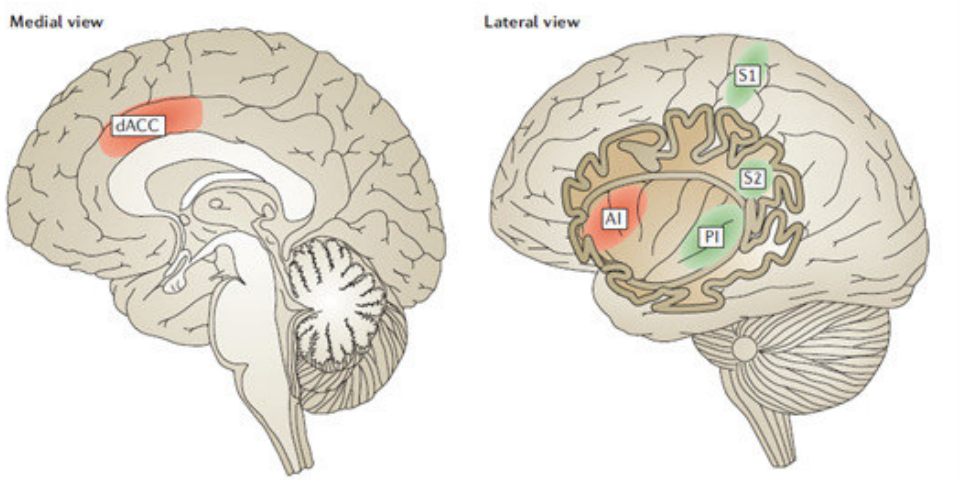
thalamic projections and might be related to many aspects of pain experience: The emotional, cognitive, motor and autonomous components. It receives projections from spinal cord and from brainstem nuclei as well as from cortical pain related areas: ACC, DLPFC, insula cortex and hippocampus (Chudler et al. 1995). Activations in basal ganglia, mostly in nucleus accumbens (NA), putamen and caudate are found when participants are exposed to experimental pain (Becerra et al. 2001; Borsook et al., 2010). Specifically, NA has been related to reward-aversion system and it shows decreased activity during pain and increases activity in pain relief. It has been also implicated in placebo analgesia (Scott et al., 2008), in transition from acute to chronic pain and it is proposed as relevant to pain modulation (Mansour et al., 2013).

Figure 1: Cortical and subcortical brain regions related do pain perception and their connections (from Apkarian et al., 2005). Primary somatosensory cortex (S1), secondary somatosensory cortex (S2), anterior cingulate cortex (ACC), insula, thalamus, prefrontal cortex (PF), primary motor cortex (M1), supplementary motor cortex (SMA), posterior parietal cortex (PPC), posterior cingulate cortex (PCC), basal ganglia (BG), hypothalamus (HT), amygdala (AMYG), parabrachial nuclei (PB), periaqueductal gray (PAG).



Pain pathways include two major pain components: The sensory-discriminative, involving the “lateral system” and the affective-motivational, involving the “medial pain system” (Albe-Fessard et al., 1985). The lateral pain system processes the sensory aspects of pain, such as intensity, quality and location. It comprises the somatosensory and parietal areas, and posterior insula. The medial pain system ensures the cognitive and affective dimension of pain and involves processing of unpleasantness experiences. It comprises the prefrontal cortex, the ACC and the anterior insula (AI).

Figure 2: The lateral pain system, processing sensory components of pain (green: primary somatosensory cortex, S1, secondary somatosensory cortex S2, posterior insula PI) and the medial pain system processing emotional-cognitive components of pain (red: dorsal anterior cingulated cortex dACC and anterior insula AI) (from Eisenberger, 2012).



Overall, these brainstem and forebrain regions have been considered as part of the “pain matrix” or the brain “pain signature” a set of specific brain areas activated under noxious stimulation, combining the different components of pain experience (Albe-Fessard et al., 1985; Ploghaus et al., 1999; Apkarian et al., 2005; Tracey et al., 2007). This recognition provided a huge development of pain studies but has also raised criticism

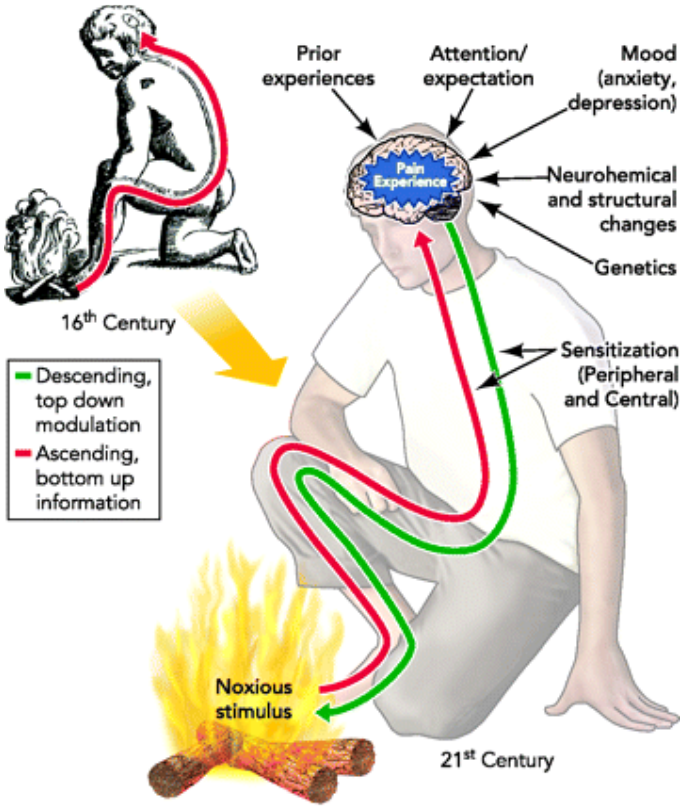
because it supposes a network specific for pain, failing to explain how these regions are interconnected during pain experience (Iannetti and Mouraux, 2010; Tracey, 2011). Thus, pain is not a sensory modality per se, and unlike the specific cortical areas dedicated to other sensory modalities, there is no "pain" center, rather multiple "pain matrixes" for the different pain conditions/sensations. A criticism to this approach is that several areas of the "pain matrix" are also activated as long has salient sensory (high arousal) and threatening information is conceived (Iannetti and Mouraux, 2010; Tracey, 2011).

Although these criticisms deserve consideration and highlight a need for more accurate concepts, they do not compromised the developing body of studies showing brain functioning under pain states and the relevance of different brain areas in its modulation.

1.1.3. Modulation

Melzack and Wall (1965) historical "Gate Control Pain Theory" was the first theory proposing an explanation concerning the absence of direct relation between stimulus intensity and the pain perceived. On its original work, the authors proposed that the spinal cord and brain could act has a gate, filtering the input of pain processing, modulating pain experience increasing or decreasing it. They believe that this occurred because spinal cord could open or close the gate depending of the activation of two opposing pathways: A nociceptive and non-nociceptive fibers (touch fibers). Even though following studies provided evidence that this was not an accurate mechanism, the Gate Control Theory highlighted the important notion that nociception is modulated along its processing pathways and that there is no direct relation between nociception and the pain experience. Since this initial proposal much more information was developed regarding these modulation mechanisms and it has been recognized the existence of a "Descending Pain Modulatory System".

Figure 3: Development of pain modulation concept (from Bingel and Tracey, 2008).



Descending Pain Modulatory System

In the dorsal horn of the spinal cord (or in the trigeminal nucleus if the information is from the head and face) peripheral neurons are forming synapses with descending neurons arising from the brain and brainstem centers. One of the most interesting fields of research on pain has been the study of these networks and their ability to modulate pain: The “descending pain modulatory system” (Tracey and Mantyh, 2007; Millan, 2002). This system can have an inhibitory (anti-nociceptive) or facilitatory role (pro-nociceptive) in pain transmission.

In this system two brainstem nuclei, PAG and RVM, play a pivotal role. Several descending pathways starting in the cortex (ACC, AI, PFC), are connected to the

hypothalamus and amygdala, and project to PAG. PAG establishes reciprocal connections to RVM, which is directly linked to dorsal horn through the dorsolateral funiculus (DLF).

In the RVM there are three types of neurons: “ON”, “OFF” and neutral. Although the functioning of the neutral neurons is still unknown (most probably they have both type of influences), it has been argued that the OFF cells are tonically active, while the ON cells increase their action when a pain stimulus arises, facilitating pain transmission. When there is no stimulation pro-nociceptive projections are not activated and the anti-nociceptive are the most useful (and as such are under the influence of OFF cells) (Fields et al., 1983; Bederson et al., 1990). When these descending projection reach the spinal cord they modulate the activity of the wide-dynamic-range neurons (and nociceptive neurons of the trigeminal nerve) from the lamina V, neurons that can be activated by nociceptive as well as by non-nociceptive information (Millan, 1999).

Beyond the PAG and RVM, other subcortical nuclei are also important for pain modulation including the nucleus tractus solitarius, the parabrachial nucleus and the dorsal reticular nucleus. Overall, these brainstem and midbrain nuclei are key elements of the descending pain modulatory system and are part of the spino-medullar-spinal loops.

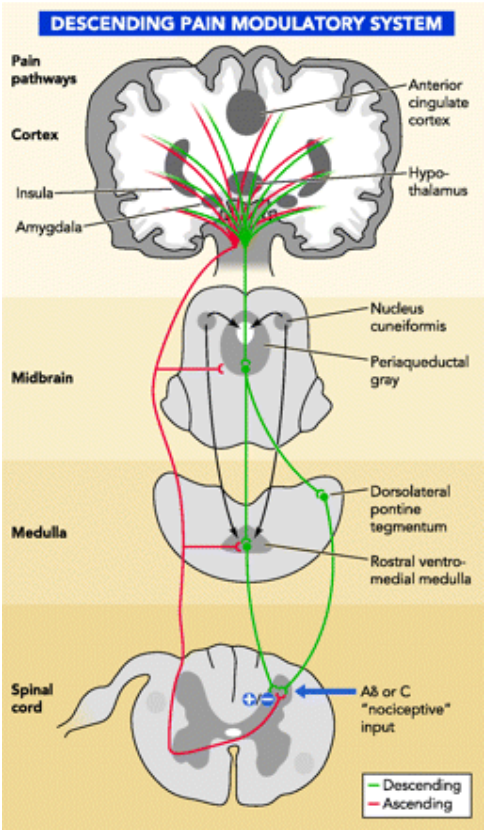
Two other pain modulation mechanisms deserve mention: One is related to the activation of motor cortex and its projection to the ventral horn of the spinal cord, and the other is the indirect impact that the sympathetic nervous system activity may have on the transmission of pain signals at the spinal cord. Thus multiple brain areas and many different descending pathways can modulate the nociception signals along its different processing stages.

The descending pain modulatory system is under serotonergic, dopaminergic and noradrenergic control and is opioid dependent (Gebhart, 2004), but many controversies still persist regarding this and other neurotransmitters functions in this system. In part this is due to the complexity of this system, expressed in its ability of both inhibit or facilitate pain signals, and also to the multiple pathways arising from different brain areas and using different neurotransmitters. Classically it has been proposed that anti-nociceptive projections to dorsal horn of the spinal cord use serotonin, dopamine, noradrenaline and opioids, while pro-nociceptive use substance P, glutamate and nerve

growth factor. However, the increased knowledge of the descending system provided evidence that the same neurotransmitter can participate in opposite actions, depending on the receptors involved in each mechanism (Millan, 2002). For example, glutamate, which is best known as the main excitatory neurotransmitter in the nervous system, has been related to increase pain processing through its NMDA receptors (Kawasaki et al., 2004). Nevertheless, another glutamate metabotropic receptor, mGluR1-8, has been related to increased activity in descending pain inhibitory pathway (Palazzo et al., 2011).

Increased evidence supports the view that cortical pain related areas controls spinal function using monoamines top-down projections. This has been considered a probable explanation for sleep, fatigue and emotional disorders usually comorbid of pain states due to the multiple roles that serotonin and noradrenaline can have on these functions (Bannister et al., 2009).

Figure 4: Schematic representation of the Descending Pain Modulatory System (from Bingel and Tracey, 2008).



Opioids

Opioids are a group of neuropeptides neurotransmitters: Enkephalins, endorphins, endomorphins, dynorphine and nociceptin. They are usually called endogenous opioids and act in several brain regions. The descending inhibitory system depends on the activity of opioid neurons, mostly through its presynaptic modulation in the spinal cord, which decreases nociceptive transmission. Inhibitory neurons arising from the PAG use opioids to induce analgesia (Park et al., 2010). Indeed, opioid injections in PAG and RVM diminishing the activity of the ON cells and increase the activity of OFF, resulting in activation of the descending inhibitory system and decrease in pain (Heinricher et al., 1992). Opioids have a major role in the placebo analgesia due to the activation of these descending inhibitory pathways (Petrovic et al., 2002). Other brain regions, such as hypothalamus, amygdala, striatum, ACC, also use opioid neurons for modulating pain signals.

Serotonin

Specifically, serotonin (5-hydroxytryptamine, 5-HT) although best known for its impact on mood, has been shown to be a key neurotransmitter in pain pathways. Due to the failure of serotonin in overcome blood-brain barrier, the peripheral and central serotonin constitutes relatively independent pools. In the periphery it is one of the elements of the "inflammatory soup", directly contributing to its pro-nociceptive effects (Godínez-Chaparro et al., 2011), but in spinal cord and in higher brain centers is actions is less clear, due to its different receptors.

One of most relevant serotonergic projections, which was believed to play a role in reducing pain transmission starts at the RVM, particularly from the raphe nucleus (Viguier et al., 2013). However, it has been recently proposed that these serotonergic descending projections may not only contribute to anti-nociception but also to pro-nociception, if persistent pain is developed (Wai et al., 2011). Accordingly, when glutamate and GABA are in balance, serotonin that usually increase pain signals on periphery is counterbalance by inhibitory descending serotonergic projections. However, when there is an increase in

excitatory pain signals from periphery (due to sensitization or other processes) this balance may be lost and the serotonin descending projections may be inhibited. Some debate still persists regarding the descending facilitatory pathway for serotonin, which is complicated by the presence of other neurotransmitters, as neuropeptides (e.g. substance P, enkephalins) and the classical excitatory (glutamate) and inhibitory (GABA) neurons in the medulla that also project to dorsal horn and that may modulate pain signals (Viguier et al., 2013).

Centrally, it is believed that serotonin (specifically the 5-HT7R receptor) can reverse the dendritic dysfunctions (increased excitatory and integration activity) in pain central brain areas, as ACC, and restore the pain sensitivity in neuropathic animal pain models (Santello and Nevian, 2015). Moreover, serotonin is also interconnected to the hypothalamic–pituitary–adrenal axis, which has also a modulating role in the pain system (Andrews and Matthews, 2004).

Noradrenaline

Another key neurotransmitter in the descending pain modulatory system is noradrenaline. Although noradrenaline may have a low relevance in healthy tissues, in case of injury it may have a pro-nociceptive role due to its ability to activate motor neurons (in the ventral horn). It has also been proposed that noradrenaline may impact on the immune system. Similarly to serotonin, it may have either anti-nociceptive or pro-nociceptive roles, depending on the class of receptor that is activated (alfa1 adrenergic receptors are pro-nociceptive while alfa2 adrenergic are anti-nociceptive). Its anti-nociceptive role occurs through presynaptic (blocking the release of excitatory neurotransmitters) or postsynaptic (hyperpolarization) actions in dorsal horn, as well as inhibiting interneurons or suppressing the action of excitatory interneurons. In higher brain centers, noradrenaline role has been not yet fully understood because, again, it may also depends on local and receptors involved (Pertovaara, 2013).

Dopamine

Dopaminergic system has been consistently associated to stress (Pani et al., 2010) and pain (Wood et al., 2007; Treister et al., 2013). Even though evidence has been provided regarding its involvement in the descending pain modulatory system (enhancing pain modulation) (Treister et al., 2013), much less knowledge exists about its ability to modulate pain in the descending system comparing to other neurotransmitters. Nevertheless, it has been observed that dopaminergic projections arising from hypothalamic nuclei to spinal cord have anti-nociceptive role through the D2 receptors (Wei et al., 2009; Taniguchi et al., 2011) and D1/D5 receptors (Yang et al., 2005). An increase in dopamine in mesolimbic and other pain related areas, as the medial prefrontal cortex and NA, is implicated in analgesia in animal models (Imperato et al., 1991; Sotres-Bayón et al., 2001). Similar findings are reported in animals subjected to social defeat (Tidey and Miczek, 1996). Dopamine also plays an inhibitory function on the ACC, and allows the inhibition of processing of pain mediated by NMDA receptors.

Recent evidence points toward a decrease in dopamine in the striatum in chronic pain (Martikainen et al., 2015). Indeed, patients with conditions related to a decrease in dopamine have pain complains, as FM (Wood et al., 2007) and Parkinson disease (Lee et al., 2006), and dopamine administration has been related to decreased pain in cancer (Dyckey and Minton, 1972) or diabetes (Ertas et al., 1998).

Other neurotransmitters

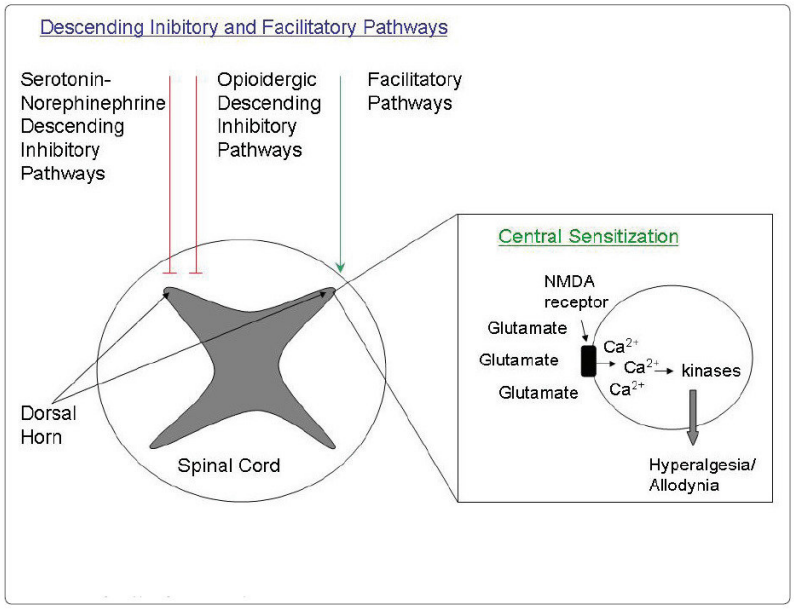
Other neurotransmitters may modulate pain through the descending pain modulatory system. One example is Substance P which is an important mediator of inflammation, increasing the function of cells of immune system, the production of pro-inflammatory cytokines and stimulating secretion of histamine from mast cells. It plays a significant role in pro-nociceptive pathways (De Felipe et al., 1998). Another example is Brain-derived neurotrophic factor (BDNF). It has been considered a key element for axonal growth and neuromodulation (Thoenen, 1995). Usually, neurons that express BDNF also express other pain modulators, for example, serotonin, substance P and

neurotensin (Yin et al., 2014). When released in the PAG, BDNF stimulates the release of neurotransmitters that increase pain signals in the RVM.

Glial Cells

Finally, it should be mentioned that the role of glial cells in pain modulation has been increasingly recognized in the later years. It has been reported an increase in cytokines, substance P, glutamate, nitric oxide and prostaglandins in microglia and astrocytes cells of the spinal cord (Watkins et al., 2001). The release of these substances by glial cells will increase the noxious transmission of nociceptor fibers in dorsal horn (Wieseler-Frank et al., 2005). Moreover, the impact of these cells at cortical level has also been found, mostly in ACC and other important brain areas of the descending pain system (Ikeda et al., 2013).

Figure 5: Neurochemical control of the descending pain modulatory system (from Lee et al., 2011).



In summary, the higher brain processing areas (e.g., prefrontal cortex, ACC, AI) communicate with the brainstem centers, specifically the RVM which receives projections from PAG. These brainstem nuclei are rich in opioid receptors and act through serotonin, dopamine and noradrenaline descending projections to dorsal horn. This, in turn, will influence the peripheral neuronal transmission. The descending pain modulatory system may have an anti-nociceptive or pro-nociceptive role. The network that allows this dual functioning has been extensively studied in the last decade, and it is now recognized that the inhibitory and excitatory processes are dynamic and may be flexible respond to different factors (behavioral, emotional, physiological) (Heinricher et al., 2009). The study of these factors may have an important impact in understanding pain mechanisms and in identification of potential therapeutic targets.

1.1.4. Perception

Increased body of knowledge has contributed to the recognition that pain is a complex experience, a consequence of several peripheral and central processes. Understanding how cognitive and emotional processes are affecting modulation mechanisms is, therefore, of greater interest (Price, 2000).

Cognitive Modulation

Indeed, emotional and cognitive factors can either potentiate or weaken pain perception. Pain perception depends on cognitive processes, as attention and distraction (Tracey et al., 2002). Given that cognitive resources are limited, it has been proposed that performing cognitive tasks can distract from pain, decreasing pain perception, mostly if these cognitive tasks have high attentional demands (Miron et al., 1989; Eccleston and Crombez, 1999; Good et al., 1999; Bantick et al., 2002). Indeed, some studies described that distraction activates the PAG, resulting in analgesia (Tracey et al., 2002) and correlates to increased connection between PAG and ACC and decreased activity of other brain pain-related areas (Bantick et al., 2002). Increased connectivity between ACC, orbitofrontal cortex and thalamus to PAG has also been found when distraction occurs

while pain stimulation is induced, suggesting the recruitment of the descending pain system (Valet et al., 2004). These results have been interpreted has indicating that pain and cognition share cognitive limited resources and that engaging attentional and control resources in a cognitive task is able to decrease the pain perception (Vohs et al., 2008).

However, other studies found different results. Seminowicz and Davis (2007) found that under intense pain stimulation, distraction tasks (high or low demanding) may not be able to significantly modulate pain. Similarly, cognitive performance may not be modulated by pain, which lead the author to argue that the brain networks for pain perception and cognitive tasks can be recruited at the same time (Seminowicz and Davis, 2007).

One possible reason for the divergent findings may be related to the differences in the cognitive tasks in use. Perhaps not all cognitive tasks significantly modulate on pain. It may depend if the task is high or low demanding, but more importantly, on cognitive processes that the task involves. Accordingly, it has been proposed that this effect may be higher for inhibitory cognitive tasks, as Stroop task, one of the most used cognitive paradigms in pain studies (Oosterman et al., 2010). This suggests that inhibitory resources are the most relevant both for cognitive tasks and pain perception. Indeed, it has been described that individuals with lower performance in inhibitory cognitive tasks were also more inefficient in the recruitment of the descending inhibitory pain system, a finding that may explain why the elderly have inefficiency in both the cognitive and pain inhibition tasks (Marouf et al., 2014).

Studies comparing these two processes found that exerting cognitive self-control in a previous high demanding tasks increase pain perception and spinal nociception (Silvestrini and Rainville, 2013). This effect occurs even after the cognitive task was finished. Using self-control resources (inhibitory) in cognitive tasks impairs the subsequent use of control resources on pain perception, even at the most basic perceptual pain physiological processes, suggesting limitation in the recruitment of the descending pain system. Further detailed studies are needed in order to fully understand how specific cognitive processes modulate pain perception.

Other cognitive processes, as beliefs, have been studied. For example, beliefs related to perceived control over pain stimulation have been related to diminished pain perception and anxiety (Kalisch et al., 2005; Wiech et al., 2006), processes that relay on activation of prefrontal cortex regions (VLPFC) (Wiech et al., 2006). These beliefs have been related to increased connections between the rostral part of ACC and PAG, a mechanism already described under distraction (Bantick et al., 2002) and placebo analgesia (Bingel et al., 2011). Similar findings have been found regarding catastrophization (Raczka et al., 2010).

Placebo analgesia

Placebo analgesia, that is, the relief in pain that occurs when an individual believes that is being subjected to a procedure or substance that reduces pain, has also been a matter of huge debate and provided knowledge about pain perception and the descending pain system (Price et al., 1999; Vase et al., 2005). Even though it is beyond the aims of the present work to go into details on this phenomenon, it is worth mention the dependence of the placebo analgesia on descending pain modulatory system. Molecularly, placebo analgesia has been linked to endogenous opioidergic system (Zubieta et al., 2005). Release of opioids has been found in pain modulation brain areas, as the ACC, the DLPFC and the PAG when the participant is under placebo analgesia (Bingel et al., 2008). The activation of this opioid system may inhibit the pain signals at the spinal cord, as already described. Pharmacological studies described that the use of an antagonist of mu-opioid receptors (naloxone) abolished placebo analgesia reaction. Moreover, the blockage of the opioid system was related to impaired activations DLPFC, rostral ACC, hypothalamus, PAG and RVM, and most importantly reduced the connectivity between rostral ACC and PAG, connections known to be essential for the descending inhibitory functions (Eippert et al., 2009). Interestingly, in this study it was found that the subjective analgesia was not completely blocked, as the subjects still reported decreased pain ratings under placebo analgesia manipulation. This may point toward the relevance of other non-opioidergic systems in pain perception, particularly the monoamine projections (it has been described the relevance of dopamine in placebo analgesia,

Schweinhardt et al., 2009) or the presence of a self-consistency bias and cognitive appraisals (Wager et al., 2006).

Emotional Modulation

Another intense aim of research is to learn about emotional modulation of pain. The effect of the emotional context on pain has been usually studied by manipulating emotions during pain induction (Villemure et al., 2003; Tang et al., 2008) based on Lang (1995) motivational priming hypothesis. This theoretical approach proposes the existence of two motivational systems: the appetitive system, which promotes positive emotions, and the defensive system, which promotes negative emotions. If a positive emotion is primed, there is higher probability of positive evaluation of an event, and if a negative state is primed, there is higher probability of a negative evaluation. In pain studies, this approach has been frequently tested using the Lang et al. (1990) International Affective Picture System (IAPS), a set of pictures with positive, negative or neutral content, that are presented while pain is induced.

Generally, it has been found that priming positive emotions decrease pain perception in healthy individuals (Meagher et al., 2001; Kamping et al. 2013; Rhudy et al., 2013). Similar findings have been reported when using different emotional stimuli, as odors (Villemure et al., 2003) or music (Roy et al., 2008). Nevertheless, results of the negative emotional priming are not so clear-cut. Although there is also a general trend toward the corroboration that negative emotions increase pain perception (e.g., Meagher et al. 2001), there has been found some interaction with arousal evoked by the situation (Rhudy et al., 2008) and many other individual differences. For example, it has been reported that under high arousal there may be a decrease in pain perception, usually called the stress-induced analgesia. Indeed, animal studies highlight that a stressful event may result in analgesia or hyperalgesia (Vidal and Jacob, 1986; Jørum, 1988) depending on a multiplicity of parameters related to individual differences (phenotypes, age, gender), the stress event (emotions induced, controllability, ability to escape) and the meaning of the environmental stress (previous experience with the stressful event) (Vidal and Jacob, 1986; Jørum et al., 1988; Butler and Finn, 2009).

Although the precise mechanisms that underlay the relation between emotions and pain are not completely understood, neuroimaging studies support the view that emotions impact on the cognitive-affective dimensions of pain, decreasing or increasing the unpleasantness of the pain experience. As such, Yoshino et al. (2010) found that manipulating the emotional context where electrical pain stimulation was induced could have a significant effect on neural responses to pain: The sad context was correlated to an increased activation in brain areas related to emotional aspects, as the ACC. Other neurocognitive mechanisms proposed emphasize the role of insula cortex in the integration of autonomic, pain and emotional processes, which may then activate descending projections to brainstem nuclei (Craig, 2002; Craig 2003a).

Another approach used in the study of emotional dimensions involved in pain perception is the investigation of individuals that show specific emotional traits, as those suffering psychological disorders (Wiech and Tracey, 2009). The affective-cognitive brain areas have been reported to be the key abnormally activated areas in individuals suffering from mood disorders. Depression and anxiety, have been associated with clinical pain complains and increased pain perception in experimental pain stimulation. It is well known that depressed patients describe pain complains (de Heer et al., 2014) and chronic pain patients describe mood disorders (Frank et al., 1988; Buckelew et al., 1994). Although a meta-analysis found that depression is related to lower sensitivity to pain, some inconsistencies have been reported (Dickens et al., 2003). Results from recent a case-control study comparing HCs and recently diagnosed (and non-medicated) major depression patients found the later demonstrated lower pain threshold and tolerance (Zambito Marsala et al., 2015).

1.2. Pain assessment

1.2.1 Pain Assessment in clinic

Because pain is a subjective experience, there are no objective measures to assess this experience in clinical or laboratory setting. It can only be assessed using observational or self-report methods. Observational methods comprise behavioral (posture, facial

expressions), functional (mobility) or vital sign assessment (respiratory and pulse rate, blood pressure, sedation) while self-report measures can inform about pain or functional impact directly asking patients.

The self-report measures include unidimensional or multidimensional measures. In the first case, the most frequently used are the numerical rating scale (NRS) and the verbal analogue scale (VAS). The numerical rating scale (NRS) simple ask a patient to choose a number that best represents its pain from “0”, “no pain”, to “10” (or 100), “the worst pain you can imagine”. The verbal analogue scale consists of continuo’s 10 cm scale and the patient can point the pain he/she experience on the scale from 0 to 10. These unidimensional scales can be used to assess pain unpleasantness ratings.

Frequently used multidimensional measures are, for example, the Brief Pain Inventory (BPI, Cleeland and Rayn, 1994) and the McGill Pain Questionnaire (MPQ), questionnaire that ask patients about several aspects of their pain: intensity, quality, relief, etc. (McGill and Togerson, 1971).

1.2.2. Pain assessment in laboratory settings

There are multiple methods to assess nociception in animal models of pain which will not be discussed herein. This section will focus on experimental pain assessment in human.

In laboratory settings pain has been studied using pain induction methods that use thermal, mechanical, electrical and chemical stimuli (Gracely, 1988). These stimuli can be applied in different body location, with variaty of durations, frequencies and intensities. For example, electrical stimulation can be applied on the skin surface or intra-cutaneous, and directed to specific nerves. Electrical stimuli can be repeated, usually have short duration and can be easily quantifiable (the electrical current can be measured). These stimuli have a clear unset and termination, but are prone to habituation effects. Another example of pain induction method in laboratory is the cold pressor test. In this test, the subjects are asked to immerse their hand in a cold water bath as much time as possible (with a safety limit). In the cold pressor test, the pain increases along the immersion. Pain

unset and termination are gradual and an interstimulation interval between two tests is needed. This method is sensitive to subjects' attention, motivation and expectations (McCaul and Haugtvedt, 1982).

Most frequently, three outcomes are collected: Pain threshold, intensity and tolerance. Pain threshold is indicated when subject report of the minimal intensity that experienced as painful. Pain intensity is most commonly collected by VAS or NPS. Pain tolerance is the maximum stimulation (intensity/time) that the subject tolerate, up to safety and ethical standards.

These measures have proven to be useful, but they also evidence some limitations because they are static measures. More recently, dynamic psychophysic models have emerged. These are based on administration of multiple stimuli, monitoring the changes in pain represent pain modulation processes. One of these methods is "diffuse noxious inhibitory control" (DNIC) paradigm that in humans was recently been renamed "conditioned pain modulation" (CPM) (Pud et al., 2009; van Wijk and Veldhuijzen, 2010; Yarnitsky, 2010). The inhibitory, anti-nociceptive, functions of the descending pain modulatory system have been studied using such methods. Excitatory, pro-nociceptive pathways are studied using the "temporal summation" paradigm.

Chapter 2

2. Chronic pain

Differently from acute pain, which is a fundamental experience for protection and survival, chronic pain is maintained for a longer period, sometimes even with the absence of the original cause. In some cases, chronic pain is a consequence of an actual injury but in many situations it is maintained long after the initial injury has been repaired. Neuroplastic changes in the nervous system maintain pain and do not allow the restore of healthy mechanism (Tracey and Bushnell, 2009).

Regardless of the etiology of the chronic pain condition, it is known that living with persistent pain has a huge impact on patients and their families, with a lot of suffering and a huge economic burden. In the USA, it has been estimated that about 100 million of individuals live with chronic pain cost 600 billion dollars to the American economy (Institute of Medicine, 2011). In Portugal, a population-based study estimated that the prevalence of chronic pain was 36.7 percent using IASP definition. Moreover, in this study it was also found that about 13 percent of chronic pain patients referred a diagnosis of depression and 49 percent indicated that chronic pain interfered in their job costs (Azevedo et al., 2012). Women, vulnerable groups with lower education and income, and the elderly were the main groups reporting chronic pain. In Portugal, global costs with chronic pain were around 2.71 percent of the gross domestic product (GDP) per year in 2010 (Azevedo et al., 2014).

It has been found that these chronic pain states may be partly reinforced by several changes in the peripheral and central nervous system. After an initial tissue damage or inflammation, different molecular mediators can develop. Stimulation of nociceptors can induce changes in ion channel function or channel expression that may be maintained spontaneously active, even if the initial stimulus is not present any longer. The channels ability to flexibly respond to environmental challenges and increase pain signals is called peripheral sensitization (Woolf and Salter, 2000). Specifically, when a

tissue is subjected to a high or prolonged noxious stimulation, the alfa-delta and C-fibers will increase the synaptic transmission at the dorsal horn of the spinal cord. This induce a removal of the Mg^{2+} that blocks NMDA (glutamate receptors) and an influx of Ca^{2+} to the cell, and production of nitric oxide. This increase in diffusion of nitric oxide has been related to a stimulation of neurotransmitter release, as substance P, from the presynaptic neuron, thus increasing the pro-nociceptive information that will achieve the second order neurons. This phenomenon will then guarantee a facilitation of nociception information, even with small stimulation (Staud et al., 2006b). The peripheral sensitization involves a lower threshold or an increase in the channels activity and, finally, an increase of synaptic transmission in the spinal cord.

Hyperalgesia can also develop after a first stimulation by a noxious stimulus. The injured area becomes more sensitive to other subsequent stimulus (in the injury site). This depends on the C-fibers activity and the release of glutamate at the spinal cord. On a more distant area around the previous injury, a second area of sensitivity frequently develops, where allodynia (secondary analgesia) occurs. Allodynia is a phenomenon in which a stimulation that in normal situations would be experienced as non-painful, will induce a painful experience. The general increased sensitivity to painful stimuli may also induce an increase in nociception in adjacent or more distant locals from the initial injury, a secondary hyperalgesia (dependent of A-fiber mediation) which imply of central sensitization.

Another possible facilitation mechanism occurs when the body is subjected to intense noxious stimulation or stimulation that is maintained with high frequency. In this case, the release of neuromodulators will trigger excitatory postsynaptic potentials that do not return to their baseline, creating a cumulative depolarization. It is called temporal summation or windup phenomenon.

In other situations, the noxious stimulation in the periphery may induce plasma extraversion near the nociceptor receptive field. This extraversion interacts with other axons and induces the release of peptides (e.g. substance P, somastotatin) and other bioactive molecules (e.g. cytokines) into the interstitial tissue, which in turn give rise to many autocrine and paracrine reactions in the surrounding tissues (e.g., vasodilation) and

the production of new inflammatory mediators (e.g., bradykinin, element of the "inflammatory soup") and reactions. These substances will send feedback to the nociceptors, activating molecular cascades that increase expression of many nociceptors and ion channels, which in turn, might change the sensitivity of nociceptors, thus contributing to persistent pain (Pezet and McMahon, 2006; Dawes and McMahon, 2013).

2.1 Changes in pain-related brain areas

The medial pain system is particularly involved in neuronal changes related to chronic pain. The ACC, repeatedly highlighted as the key area in processing the unpleasantness of painful experience (Apkarian et al., 2005) and inhibitory processes (Spunt et al., 2012), is highly activated in chronic patients under resting state and in pain that is induced experimentally (Baliki et al., 2006; Kulkarni et al., 2007; Baliki et al., 2008). Therefore, when this structure is sectioned in highly severe and intractable chronic pain states, it is found that, although the individual reported the presence of pain he no longer feels "annoyed" by it.

As already mentioned, the AI being an important area for interoception and for processing bodily unpleasant sensations, has been related to clinical pain, but also with various negative physical states as irritable bowel syndrome, fatigue, frequent in chronic pain conditions (Craig, 2003b; Critchley et al., 2004). It has been proposed that this region detects aversive physical signs and it may trigger negative thoughts, avoidant behaviors and anxiety, thus contributing to the amplification of pain (Paulus and Stein, 2006). In animals, it was found that the AI establishes connections with many brainstem structures that are part of the descending inhibitory system (Fields, 2005), which may explain their amplifying effect. Yet increased activation of AI may be a fundamental characteristic of chronic pain conditions (Cook et al, 2004; Witting et al, 2006; Napadow et al., 2010).

Another key area in chronic pain is the dorsolateral prefrontal cortex (DLPFC) that acts as a control region for dorsal ACC and is also important in controlling physical pain (Lorenz et al., 2002). Recently it has been proposed that altered connectivity between insula cortex and DLPFC may be a hallmark of altered brain function in chronic pain states

(Ceko et al., 2015). Interestingly, this recent study showed evidence that this abnormal pattern of connectivity can be reversed months after some therapy (Ceko et al., 2015).

Growing body of evidence of animal models and humans increasingly recognized the relevance of mesocorticolimbic brain circuitry on chronic pain (Navratilova e Porreca, 2014). Mesolimbic structures function has key regions for balancing the relevance of different motivations and developing actions toward goals. Indeed, these regions modulate pain because pain is an aversive state that must be rapidly overcome (avoidance). Relief of pain is a high motivation as may be the search for positive states (approach). In chronic pain it has been described as increased connectivity between NA and prefrontal cortex (Apkarian et al., 2011) as well as changes in gray matter in prefrontal cortex, ACC and NA, suggestive of emotional learning of pain and altered motivation responses. Behavioral support from this view has also been collected: chronic pain patients show problems in decision making and reward tasks (Apkarian et al., 2004a; Walteros et al., 2011) and it has been described that they make more impulsive risky monetary choices in a gambling task than HC (Berger et al., 2014). Following a similar trend, a study with animal models of chronic pain found that these animals would stop to seek food reward if it became harder to obtain, something that did not occurred in the healthy group (Schwartz et al., 2014). The changes found in chronic pain correlated with changes in dopaminergic neurons in the NA and the interaction with galanin, a neuropeptide receptor. Thus NA, ACC and RVM may have a pivotal role in the neuroplastic changes that occur in chronic pain states due to persistent nociceptive input (Porreca et al., 2002).

Recent longitudinal studies of subacute pain patients described that the patients in a subacute state that would end in persistent pain after one year, showed at baseline, a reduction in connectivity between NA and prefrontal cortex, suggesting that abnormal motivational networks may make individuals more prone for chronic pain (Baliki et al., 2012). Other longitudinal studies from the same team comparing brain activations between those of the subacute group that recovered with those that maintained persistent pain after one year showed that, after this year, in the first group there was an overall diminishing activity in brain pain-related areas, while in the persistent pain group the activations became stronger in emotional brain areas (Hashmi et al., 2013). Another

longitudinal study found changes in connectivity between hippocampus and prefrontal cortex, which suggest changes in learning and emotional process, frequently highlight complains of chronic pain patients (Mutso et al., 2014).

Overall, studies in chronic pain populations have shown that emotional brain regions as ACC, insula, prefrontal cortex, NA, are the key regions implicated in the transition from acute to chronic pain and are prone to structural changes, with significant loss of gray matter volume (Apkarian et al., 2004b; Schmidt-Wilcke, 2008, Baliki et al., 2011; Kregel et al., 2015), changes in white matter connectivity (Ivo e al., 2013; Mansour et al., 2013) and functional changes in chronic pain conditions (Baliki et al., 2008; Cauda et al., 2009a; Geha et al., 2008; Malinen et al., 2010; Baliki et al., 2012; Kong et al., 2013; Loggia et al., 2013).

2.2 Fibromyalgia

FM is a widespread chronic pain syndrome which diagnostic criteria was defined by the American College of Rheumatology in 1990 and was recognized as a chronic rheumatic syndrome by World Health Organization in 1992. The original 1990 criteria define FM has widespread musculoskeletal pain, with no joint or inflammatory involvement (Wolfe et al., 1990). According to this classification, FM is characterized by a history of widespread pain (symmetrical, affecting either the upper or lower part of the body, as well as the axial skeleton) and the presence of pain on digital palpation, with a force of about 4 kg in 11 of 18 points (in the occipital areas, lower cervical, trapezius, supraspinatus, second rib, epicondyle, gluteal, greater trochanter and knee).

It has been more than 25 years since the first recognition of this syndrome by a scientific society, and debate is still open about its definition and pathophysiology. Recently, new preliminary diagnostic criteria for FM were proposed (Wolfe et al., 2010). These new criteria exclude the tender point examination, which was considered difficult to assess in primary care settings and highly correlated with psychological distress (Wolfe, 1997). A survey questionnaire has been developed, based on severity and its key symptoms: pain, morning stiffness, fatigue and cognitive problems (Wolfe et al., 2010).

Overall, FM patients have pain and fatigue as major complaints, but beyond these two, there is usually a high amount and variety of health problems. The most frequently are sleep problems, morning stiffness, neurological and mental symptoms (for example, impaired memory and concentration, depression and anxiety), gastrointestinal (e.g., irritable bowel syndrome), urinary and genital (for example, frequent urinary infections) (Williams and Schilling, 2009). The symptoms differ from patient to patient and within the same patient during the course of the syndrome.

The estimated global mean prevalence (worldwide) of FM using 1990 diagnostic criteria was set about 2.7 percent (4.2 percent for women and 1.4 percent for men; Queiroz, 2013). The female to male ratio was 3:1. In Portugal the overall prevalence is 3.6 percent, with 5.2 percent for women and 1.8 percent for men (Branco et al., 2010). Using the 2010 modified criteria, which uses the survey questionnaire that does not require the tender point examination, the prevalence was considered similar (Wolfe et al., 2013), but it has been argued recently that it may be higher (Jones et al., 2015). FM has been considered most prevalent between the 3rd and 5th decade of life or even later (Wolfe et al., 2013) but there has been increased reports of earlier onset (Vincent et al., 2013), including in children (for example, in Mexico, prevalence in children between 9-15 years old was set about 1.2 percent using 1990 diagnostic criteria; Clark et al., 1998). It is also considered most prevalent in areas with lower education and lower social-economic status (Mas et al., 2008).

The study of comorbidities in FM shows evidence of depression and other psychological disorders as well as neurological diseases, cardiovascular conditions, endocrinological disorders (diabetes, thyroid diseases), respiratory problems (lung diseases, asthma), urogenital, gastrointestinal disorders and allergies. It is also well established that FM is highly prevalent in Rheumatic disorders (Wolfe, 1997). The recognized presence of the FM in many chronic pain patients has led to the recent proposal that this syndrome may be an ending point of many chronic pain conditions (Clauw, 2015).

2.2.1 Studied mechanisms

Several lines of evidence showing abnormalities in different body systems have been studied. One of the most debated were the sleep disturbances, evident in the interference of awakening waves in the deepest non-REM sleep phases (the called alfa-delta sleep pattern) (Moldofsky et al., 1975). Inducing a similar pain pattern in healthy volunteers causes pain, fatigue and tenderness complaints that resemble FM symptoms (Moldofsky et al., 1976). Poor sleep quality has been associated with less efficient pain descending inhibitory system in healthy (Ablin et al., 2013) and FM (Paul-Savoie et al., 2012) individuals. Overall, some authors proposed that sleep dysfunction might be a fundamental mechanism underlying FM pathophysiology (Moldofsky, 2008; Choy, 2015).

It is important to note that FM patients show altered functioning of the hypothalamic-pituitary-adrenal (HPA) axis and some authors have been discussing its impact on the etiopathogenesis of the syndrome (Adler et al., 1999; Wingenfeld et al., 2010). Most frequently there have been descriptions of a pattern of low cortisol during the morning and daytime. This pattern is suggestive of hypocortisolism (Riva et al., 2010). But the specific nature of the changes in the HPA axis found, have not been clear-cut (Webster et al., 2002; van Rossum et al., 2006). Moreover, FM patients' evidence significantly changes in the production of hormones (growth hormone, prolactin, cortisol, etc.) (e.g. McBeth et al. 2005; McLean et al., 2006; Weissbecker et al., 2006; Tanriverdi et al. 2007). The specific causal role of these changes in the syndrome has yet to be determined.

There have also been described dysfunctions in many transmitter systems in cerebrospinal fluid or plasma of FM patients (e.g., serotonin, noradrenalin, dopamine, substance P, etc., for a review Becker and Schweinhardt, 2012). For example, increased concentration of substance P (Russell and Littman, 1994; Bradley and Alarcón, 1999; Russell, 2002) and increased concentration of neurotrophic factors such as NGF (Giovenco et al., 1999) and BDNF were found in FM patients, regardless of the presence of a depressive disorder (Laske et al., 2007). It is also extensively described as a decrease in the concentration of serotonin, the neurotransmitter that in addition to its known effect on the etiology of depression has an important role in the functioning of descending

system by inhibiting the production of substance P and amino-excitatory acids in the spinal cord (Woolf and Salter, 2000). This decrease of serotonin may also be related to allodynia phenomenon (Russell et al., 1992). Changes in the concentrations of these neurotransmitters are in line with evidence of decreased pain threshold and pain abnormalities (Kosek et al., 1995).

The importance of psychological factors in FM syndrome has also been extensively studied. It has been described that these patients have high rates of childhood trauma and multiple traumatic life events (Goldberg et al., 1999; McBethet al., 1999), lifetime psychiatric co-morbidity (Arnold et al., 2006), higher levels of stress, as measured by daily hassles than RA patients or control subjects (Dailey et al., 1990) and deficits in positive affect regulation (Zautra et al., 2005). About one third of the patients are depressed (Walker et al., 1997; Okifugi et al., 2000; Hudson et al., 1992). However, it is noteworthy that most of FM patients (between 65-75 percent) do not reach criteria for any psychiatric disease when assessed in specialized care, which suggests that in the general population, psychiatric diseases in this group will be even less frequent (Yunus, 2015). A recent study suggested the presence of different profiles of FM patients, one with high psychopathological problems and another with much less (Gonzalez et al., 2015). Thus, it is still unclear how far psychological disorders, traumatic experiences and other emotional variables can contribute to FM unset and development.

It has also been proposed that FM may be a disorder in the functioning of the autonomic nervous system with deregulated activity of the sympathetic system and imbalance and lack of coordination between the sympathetic and parasympathetic nervous system (Bengtsson A. and M. Bengtsson, 1988; Martinez-Lavin and Hermosillo, 2000). A predominance of sympathetic nervous system activity has been evidenced in heart rate variability, skin response and genetic studies (Martinez-Martinez et al., 2014). Nocturnal heart rate variability analyzes which evidence a predominance of sympathetic activity in FM patients has been indeed proposed has a biomarker of this syndrome (Lerma et al., 2011). However, this pattern of sympathetic activity may be a key mechanism shared with other functional disorders, frequently comorbid with FM, as irritable bowel syndrome and interstitial cystitis (Petzke and Clauw, 2000; Martinez-Martinez et al., 2014) and methodological quality of these studies may argue against the

proposal of a specific role of Autonomous Nervous System dysfunction in the pathophysiology of FM (Tak et al., 2009).

More recently, the role of peripheral mechanisms in the pathophysiology of FM have been a highlight. One example of this line of research has been the study of small fiber neuropathy (Oaklander et al. 2013; Kosmidis et al., 2014). Skin biopsies (Oaklander et al., 2013; Kosmidis et al., 2014; Caro and Winter, 2014) and corneal confocal microscopy (Ramirez et al., 2015) of FM patients' evidence decreased small nerve fiber density. Reduced axon diameter in skin biopsies has been found suggesting a possible specific profile of dysfunction that should be cleared in future studies (Doppler et al., 2015). Overall, these findings show that small fiber neuropathy may induce pain in FM and that the pain may be, at least be in part, a consequence of peripheral immune processes (Caro and Winter, 2014).

There is also evidence of other mechanisms of abnormal nociception in this syndrome (e.g. Staud et al., 2006b). Patients with FM describe pain as widespread and refer to the musculature and deep tissue. Although it was claimed that FM is not a muscle disorder (Simms, 1998), some abnormalities have been described lately and authors have been arguing that muscle abnormalities may have an important role in FM pain (Staud, 2006a). Muscle biopsies of FM evidence showed atrophy of type II fibers, less capillaries and mitochondrial volume density (Kalyan-Raman et al., 1984; Yunus et al., 1988). Several studies showed deficiencies in red fibbers, specifically, ragged and inflammatory signals, ischemia and tension (Pongratz and Späth, 1998). Studies using microdialysis techniques showed that there was increased serotonin, glutamate, lactate, and pyruvate in muscles of FM patients (Gerdle et al., 2014) and elevated cytokines (IL-1) (Sprott et al., 1998), suggesting altered milieu of the nociceptors, which may sensitize these receptors and increase the peripheral abnormalities in pain processing. Decreased ATP, and phosphocreatine/inorganic phosphate ratio have also been described (Bengtsson et al., 1986). Moreover, changes in functional aspects of muscles (as conduction velocity and fatigue) have been reported and play a role in the described abnormal muscular relaxation (Bazzichi et al., 2009). Accordingly, there is a large body of evidence showing that FM patients show increased sensitivity to painful as well as non-painful stimuli in

different modalities, as cold, heat, sound, smell, chemicals and mechanical stimuli (Lautenbacher et al., 1994; Geisser et al., 2008).

Overall, both peripheral and central mechanisms may contribute to the increased pain complains and there is evidence of both secondary hyperalgesia and allodynia (Staud et al., 2009). This data has been corroborated by functional magnetic resonance studies showing an abnormal (usually augmented) neural response to pain in several brain areas related to pain processing (e.g., Cook et al., 2004). We will describe this data in the next sections.

2.2.2 Structural findings

As mentioned for chronic pain in general, sustained neuronal activations in chronic pain conditions may be related to a decrease in gray matter volume (Apkarian et al., 2011). Several morphometric studies found similar results in FM (Schmidt-Wilcke et al., 2008; Kuchinad et al., 2007; Hsu et al., 2009). One of these studies found that FM patients have lost three times more gray matter than it was supposed in normal aging and each year of FM increased ten folds the gray matter lost (Kuchinad et al., 2007). Other studies did not support such a large effect (Schmidt-Wilcke et al., 2008) and suggested that this loss may be higher in patients that have also psychological disorders (Hsu et al., 2009). When comparing a FM group with those with or without psychological disorders, it was found that the first had a significant loss in gray matter in insula cortex and the loss was correlated with anxiety but not with clinical pain reports. The authors suggested that this loss may be related to atrophy due to the increased role of insula in psychological disorders or due to a lack of participation of this brain area in positive emotions (Hsu et al., 2009).

Overall, the brain areas with reduced gray matter reported in the structural fMRI studies are similar to those found in other chronic pain conditions: ACC, thalamus, prefrontal cortex and insula. These changes in gray matter and white matter are usually correlated with clinical symptoms. For example, it has been reported that changes in thalamus, ACC and insula were related to stress symptoms while changes in prefrontal

cortex were related to pain and fatigue (Lutz et al., 2008). Prefrontal cortex (and mid-prefrontal cortex) changes have been also correlated with cognitive performance (working memory and long-term memory tasks) (Luerding et al., 2008).

Moreover, white matter reductions in FM patients in the thalamus have also been described (Lutz et al., 2008; Sundgren et al., 2007). The reductions correlated with pain and dysfunctional external beliefs about pain (Sundgren et al., 2007).

2.2.3 Functional findings

Neuroimage studies in rest showed diminished regional cerebral blood flow in the thalamus of FM patients (Mountz et al. 1995; Kwiatek et al., 2000). This has been interpreted as indicating less responsiveness of thalamus and a diminished ability to recruit the descending pain inhibitory system (Kwiatek et al., 2000; Jensen et al., 2009).

Based on rest connection patterns that led to the definition of so-called DMN (default mode network) and EAN (executive attention network), Napadow et al. (2010) found changes in the connectivity between these two neural networks (by comparison with MVN, medial visual network) in FM patients and healthy individuals. The authors explained that patients showed an increase in connectivity in the DMN and right EAN and an increased connection between these networks and the insular cortex. In addition, positive correlations were identified between these changes and the increased intensity of spontaneous pain in these patients. It was also observed a higher connectivity in the right EAN with the PAG and a lower intensity of pain. These results remained similar when the FM group was separated according to number of symptoms of depression. This suggests that insula hyperactivity may be a central feature of brain activation patterns of pain in FM. This study also found that the higher activations occurred in almost the entire territory of the insula encompassing more posterior areas, which are believed to be related to the encoding of the intensity of painful stimuli, and the anterior insula, which play an important role in integrating emotional aspects and on pain anticipation. The reported increase in connectivity between right insula and EAN, and changes in connectivity to PAG compromise the functioning of the EAN and the cognitive control of

pain. These are probably related to the reported changes in working memory and attention attributed to patients with FM (Glass et al., 2011) and patients with chronic neuropathic pain (Cauda et al., 2009b).

Later studies supported the argument that there may be a different network organization in FM patients comparing to HC reflected in an increased connectivity between insula and cingulate cortex (Ichesco et al., 2014). Data with fMRI brain activations under experimental pain showed that the pattern was similar to other chronic pain syndromes: FM patients have demonstrated the same activated pain related brain areas (insular cortex, ACC and prefrontal cortex) as HC, but this occurred at lower stimulations intensities (Gracely et al., 2002; Cook et al., 2004). However, when high intensities stimulus are used (NPS>70), even adjusting intensities with subjective pain ratings, there is an increase in the AI and ACC in FM patients comparing to HC (Pujol et al., 2009). Heightened activations in these regions, plus thalamus and prefrontal cortex and SMA were also found in FM using a tonic pain paradigm even in the anticipatory phase (before pain stimulation) (Burgmer et al., 2009) or under non-noxious stimulation (Cook et al., 2004).

One study reported a decrease in activation of the rostral ACC (Jesen et al., 2009) that was related to a decrease in the connectivity with hypocampus, amygdala and RVM, as well as between thalamus and orbitofrontal cortex. This was taken has a direct support for a deficit in descending pain modulatory system (Jensen et al., 2012). Moreover, altered brain activation and connectivity in key areas of descending modulatory system (Burgmer et al. 2010; Cifre et al., 2012) were found, specifically between the rostral ACC and brainstem areas (Jensen et al., 2009; Jensen et al., 2012).

Recent studies of pain anticipation and relief have indicated deficient activation of pain areas relevant for pain modulation, as PAG, during anticipation of pain, as well as decrease activation of ventral tegmental area in anticipation, stimulation and pain relief in FM patients (Loggia et al., 2014). Furthermore, it has been also reported that the impact of cognitions (as catastrophizing) might be mediated by the recruitment of lateral prefrontal cortex during the anticipation of pain (Loggia et al., 2015). Again, the reduced activation of this brain region suggests that FM patients have decreased ability in

modulating pain in response to cognitive or emotional manipulations. Studies of brain activation patterns of painful stimulation also indicated that even before a thermal noxious stimulus is applied, participants with FM showed a higher activation than HC in AI (Cook et al., 2004).

2.2.4 Neurochemical findings

The rostral ACC is also known for its mu-opioids receptors. Harris et al. (2007) found a decrease in mu-opioid receptor binging in the cingulate, amygdala as well as striatum and NA of FM patients. These changes were negatively correlated to affective pain dimensions, and corroborate the lack of usefulness of opioid medication in this syndrome (Baraniuk et al., 2004). It has been suggested that persistent on-going pain provokes sustained opioid activations, which could induce downregulation of its receptors as a consequence.

Other dysfunctions in neurotransmitters system in these brain regions have been reported. For example, an increased glutamate concentration in the insula was found and correlated with pain in these patients (Harris et al., 2009). This increase has been considered to have a probable mechanism for atrophy of gray matter in this area due to the high excitotoxicity of this neurotransmitter (Mattson et al., 1989; Petrou et al., 2008). Several studies have been suggesting an increase in the glutamatergic system in pain modulation brain regions (Fayed et al., 2010; Feraco et al., 2011; Valdés et al., 2010). In fact, it was reported that the baseline hypoperfusion (Guedj et al., 2006) could be reversed by good respondents of ketamine administration (an NMDA receptor antagonist). A decrease in glutamate at insula occurred after acupuncture in these patients (Harris et al., 2008). On the opposite, diminished GABA in insula was found to be correlated with pain ratings (Foerster et al., 2012).

There is also evidence of deficiencies in the dopaminergic circuitry essential for activation of the descending pain modulatory system and the inhibition of pain (Wood et al., 2007). Specifically, there were changes found in the metabolism of presynaptic dopamine in areas such as the midbrain, the thalamus, hippocampus, parahippocampal

gyrus, ACC and insula. Differently from HC, FM patients show reduced release of endogenous dopamine in basal ganglia in response to experimental tonic pain induced by intramuscular infusion of hypertonic solution. These findings may be due to a lower level of receptors in patients with FM or a greater base dopaminergic tone. Finally, it was also observed that dopamine metabolism correlated with the decrease in gray matter density in cingulate cortex (Wood et al., 2009). These deficiencies may also be found in other neurotransmitters, as previous studies reported a blunted serotonergic system and also decreased activity of the noradrenergic projections tracks (Russell et al., 1992).

2.3 Differences between FM and other Rheumatic diseases

FM was often considered an element of a group of syndromes that included irritable bowel syndrome, migraine, myofascial temporomandibular disorder, chronic pelvic pain, etc., which has sensitivity to pain as a major complain. Classically the sensitivity to pain in these syndromes has been related to psychological distress and the absence of tissue damage (Ablin and Clauw, 2009). This has led to the categorization of FM as a “functional syndrome”, a “medically unexplained disease”, “idiophatic” and a “somatization disorder” (Yunus, 2008). Based on the increased body of knowledge regarding peripheral and central pain mechanisms in these syndromes, and on the recognition that psychological factors have an impact in any pain condition or disease (Carlino et al., 2014), it has been recognized that all of these syndromes may be more accurately considered to have central sensitization conditions and that the previous categorizations should be abandoned (Trief et al., 1987; Lee et al., 2014; Yunus, 2007; Yunus, 2015).

American College of Rheumatology recognized the need to change paradigms and developed a task force for increasing the knowledge regarding pain mechanisms and pain management across rheumatic diseases (Borestein et al., 2010). In fact, central sensitization mechanisms of pain described in FM have not yet been so extensively investigated in other rheumatic pain conditions (Lee et al., 2011; Phillips and Clauw, 2013). Conditions such as Osteoarthritis (OA) and RA have an important joint and inflammatory component, but only recently increased evidence suggested that central

sensitization mechanisms, well described in FM, contribute to pain perception in these patients (Brown et al., 2014; Yunus, 2015). On the contrary, it has been recognized that central sensitization has a key role in FM syndrome, but as already mentioned in the previous sections, only recently there has been recognized the contribution of peripheral mechanisms (Vierck, 2006; Staud et al., 2009; Oaklander et al., 2013).

Moreover, the recognition of poor correspondence between pain complaints and structural lesions in rheumatic diseases suggests that similarities between these conditions that involve pain may be higher than initially expected (Creamer and Hochberg, 1997; Bedson and Croft, 2008). In fact, similarly to what was found in FM (Lautenbacher et al., 1994) individuals with RA (Huskisson and Hart, 1972; Konttinen et al., 1992) and OA (O'Driscoll and Jayson, 1974; Kosek and Ordeberg, 2000; Gwilym et al., 2009) also show evidence of increased pain in response to experimental pain when compared to HC on the lesion sites but more importantly in other non-painful sites. Moreover, increased temporal summation previously described in FM was also found in RA (Wendler et al., 2001) and OA (Arendt-Nielsen et al., 2010).

Neuroimage studies comparing brain activations under pain stimuli have shown that similarly to what is found in FM and other chronic pain conditions (Kregel et al., 2015), RA and OA patients also indicate evidence of increased activations of the medial pain system when subjected to experimental pain (Jones and Derbyshire, 1997; Kulkarni et al., 2007; Jones et al., 2012; Lee et al., 2014). One study tried to use an innovative neuroimage technique of functional connectivity as a diagnosing tool for RA and FM but failed to significantly distinguish between the two disorders (Sundermann et al., 2014). Additionally, receptors binding of mu-opioid in the medial pain system, in the ACC and AI in FM (Harris et al., 2007) were also reported in RA (Jones et al., 1994).

Table 1: Sensory testing of peripheral and central mechanisms in fibromyalgia, osteoarthritis and rheumatoid arthritis (from Lee et al., 2011).

	Peripheral findings	Central findings			
	Low pain thresholds at affected sites	Low pain thresholds in a widespread distribution	Loss of descending analgesia (conditioned pain modulation)	Temporal summation	Expanded areas of hyperalgesia
Fibromyalgia	X	X	X	X	X
Osteoarthritis	X	X	X	X	X
Rheumatoid arthritis	X	X		X	X

Nevertheless, there is also evidence of differences between these rheumatic conditions. For example, Burgmer et al. (2010) found that FM and RA patients show different brain activations in response to evoked pain. In FM the activations rely significantly more on prefrontal and cingulate brain areas than RA individuals. Moreover, using CPM paradigm contradictory findings regarding CPM magnitude have been reported in RA. Leffler et al. (2002) did not show significant differences in CPM comparing to HC while in OA (Kosek and Ordeberg, 2000; Arendt-Nielsen et al., 2010) and FM (Kosekand Hansson, 1997; Julien et al., 2005), there has been reported the deficient pain modulation. Another study investigating the pain modulation in response to exercise also found that RA patients show evidence of normal exercise-induced analgesia, while FM did not (Meeus et al., 2015).

2.3.1 Emotional modulation of pain in FM and other Rheumatic diseases

As described in the previous section, neuroimaging studies provided evidence that under pain stimulation, FM patients and RA or OA patients showed increased activations of the medial pain system. This system, related to the effective dimensions of pain, is particularly related to depression and anxiety that is frequently part of the chronic pain mechanisms.

Studies regarding the impact of depression in chronic pain patients found that the more depressed the patient is, the more activation is found in the AI and amygdala and the less activation is found in prefrontal cortex. Giesecke et al. (2005) described that the

FM patients who had been diagnosed with depression showed evidence of increased activation in the amygdala and AI. Clinical pain was also related to an increase in the magnitude of activation of the insula, the ACC and the prefrontal cortex. Schweinhardt et al. (2008) found a similar result in patients with RA who suffered from depression; depression correlated with the prefrontal cortex activation. The PFC activations mediated the relationship with the number of joints affected by the disease. Another interesting finding from this study was that there was significant correlation between depression and number of tender points in RA patients, suggesting a similar pattern with FM. In OA patients it has also been shown that the engagement of emotional brain areas may be correlated with pain (Kulkarni et al., 2007; Parks et al., 2011).

Another emotional variable frequently explored in pain studies is beliefs about pain and pain anticipation. Gracely et al. (2004) found that the group of FM patients that had higher catastrophization scores showed increased neuronal activation in the medial pain system. However, a similar pattern is found in healthy individuals and other chronic pain conditions, such as RA (Penhoat et al., 2014), and it seems that beliefs related to catastrophization of pain can be present in any individual and are not characteristic of a specific disease (Yunus, 2015). Concerning anticipation of pain, at least one study directly compared FM, OA and HC. It was found that both clinical groups reported abnormal anticipation with increased activity in insula and prefrontal cortex (Brown et al., 2014). The insula activations were correlated in both groups with clinical pain and activations of the PFC were negatively correlated with psychological coping.

Despite the extensive literature relating pain with psychological disorders, few studies used neuroimaging to investigate the effect of specific emotions in pain modulation in different FM or other rheumatic pain conditions. One exception was a study that investigated the emotional pain modulation in FM, RA and HC when viewing pictures with emotional content (Rhudy et al., 2013). It was found that only in the FM group there were deficits in emotional modulation of pain, and that this deficit was specific for positive emotional pictures. Another study found similar results comparing FM and HC (Kamping et al., 2013) suggesting that deficits in pain modulation may be more pronounced in FM than in RA and may be more specifically for positive emotional

modulation. Additional studies are needed in order to fully corroborate and understand these differences.

Increased emotional pain in brain-related areas may be part of the chronic pain condition, increasing the duration of pain and at the same time, exacerbating and maintaining it (Tracey et al., 2009, Apkarian et al., 2013). More recently, it has been proposed that this pattern of activations (and the fact that multiple symptoms of FM and central sensitization are present in other chronic pain conditions) may be suggestive that FM may be an end point for other pain conditions when the central nervous system undergoes changes in pain mechanisms (Clauw, 2015).

2.3.2 Social modulation of pain in FM and other Rheumatic diseases

Individuals with chronic pain have increased levels of emotional disturbances, which are often associated with changes in their proximal social sphere (neglect and / or family violence, divorce, isolation, loss of social roles, etc.) (Goldenberg, 2010; Kool and Gennen, 2012). Moreover, the social support is usually related to an improvement in the health status and a decrease in pain levels (Uchino et al. 1996; Bootheby et al., 2004; Cano et al., 2005; Lopez-Martinez et al., 2008), although other studies indicate the opposite (Flor et al., 1987; Kerns et al., 1990). However, it is beyond the scope of the present work to detail the theoretical aspects of social support on the realm of pain study.

Studies regarding the social support on rheumatic conditions describe that FM patients have more loneliness feelings and feel less social support comparing to RA patients (Kool and Geenen, 2012). However, a recent study found that the perception of restrictions in social activities have a high impact on pain, fatigue, functional disability, depression and anxiety in RA patients, both in early and established patients. In the established sample it also relate to disease activity and self-esteem (Benka et al., 2015).

Few studies have been assessing the impact of social dimensions on pain. One exception was a study that compared the effect of social support through the presence of a significant person while patients with FM and migraine were in pain (Montoya et al.,

2004). A decrease in pain ratings was found when the individual is in the presence of a significant person. This effect was larger in the FM group and only occurred when the painful stimulation was applied to a tender point. Interestingly, it is worth mentioning that in this study, patients with FM showed evidence of less catastrophizing than the migraine group.

Chapter 3

3. Social modulation of pain

3.1. Social pain/social distress theory

Among several emotional variables, it has been proposed that social distress may have a higher role than negative emotions in pain modulation. This may occur because in humans, as in other animals, whose life is based on social organization, threats to social connections may be as challenging as physical pain (Panksepp, 1998; MacDonald and Leary, 2005; Eisenberger and Lieberman, 2004). Mammalians develop in social groups and depend not only on good physical health but also on good social integration. In these animals, the connection to a social group is essential for survival, because it ensures protection, mating, as well as searching and sharing of resources. Particularly in humans, the long period of reliance on parents' protection suggest the importance of developing biological mechanisms in order to maintain social connections. Bowlby (1973) studied this system, the "attachment system", and showed the importance that a safe relationship between caregiver and baby, may not only impact the emotional well-being in childhood but also during adulthood.

In the last few decades, several studies have supported Bowlby's (1973) view, showing that situations involving rupture of significant social relationships are very significant for mental (Monroe et al., 1999) and physical health (Mikulincer and Florian, 1998). In addition, it has been corroborated that social support has a strong role in clinical outcomes in many acute (Brown et al., 2003) and chronic pain conditions (Phillips and Gatchel, 2000). Social distress events (e.g. divorce) are the life events that are mostly involved in depression disorder and have a higher ability to trigger this condition than events less related to social world (e.g. loss of employment) (Kendler et al., 2003).

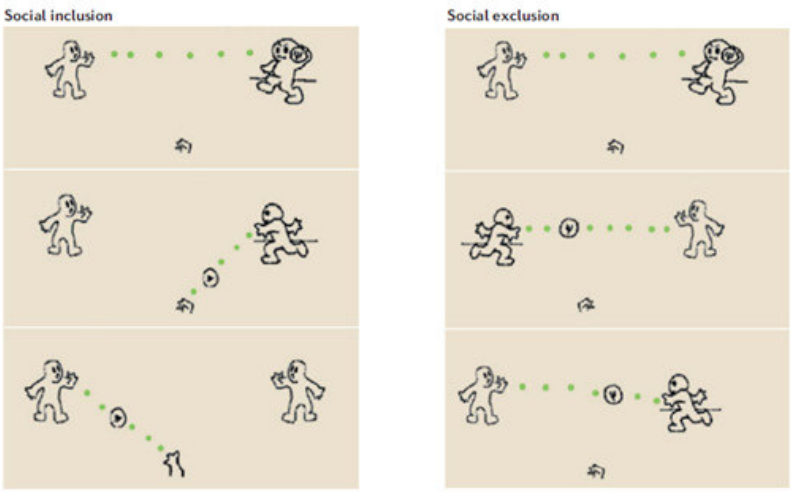
Social distress has also been consistently related to physical pain complaints (for a review Landa et al, 2012). The social distress events trigger increased reactivity of the hypothalamic-pituitary axis which regulates the neuroendocrine stress responses (Dickerson and Kemeny, 2004). Similarly to physical pain, social distress events increase proinflammatory cytokines (cells related to inflammatory response) and increase cortisol response (hormone whose production increases under stress). Thus, social distress events trigger changes in neuroendocrine parameters and promote the production of pro-inflammatory cytokines, predisposing individuals to disease and promoting a "sickness behavior" involving apathy, depressed mood and social isolation (Dantzer et al., 2008). An obvious vicious cycle, which is often recognized in the social behavior of individuals with various diseases, such as those related to chronic pain (Kool & Gennen, 2012).

Based on Panksepp (1978) approach with his animal studies, which showed that separation cries of a guinea pig could be relieved by administration of opioids, Eisenberger et al. (2003; Eisenberger and Lieberman, 2004) searched for the similarities between physical and social processes, more specifically, between physical pain and “social pain”. Social pain has been described as the suffering occurring when a significant social relationship is damaged, lost or threatened (Eisenberger et al., 2003). According to the authors, the similarities between physical and social pain can be found for example, in the frequently used verbal expressions, such as "broken heart" or "I was hurt" referring to physical dimensions the experiences related to the social sphere (Macdonald and Leary, 2005). They proposed that the attachment system may have co-opted the resources of the pain system to signal potential risk to the individual. In fact, Bowlby (1973) has argued, based on its attachment theory, that the inability to receive support heightens anxiety about the ability to receive support from the caregiver, resulting in difficulties in relationships and low self-confidence throughout life. Thus, Eisenberger et al. (2003; Eisenberger and Lieberman, 2004) proposed that due to the recruitment of similar neurocognitive resources, individuals who are more anxious about the availability and affect from others would also be prone to react with distress to physical pain.

In 2003 part of this prediction was tested by Eisenberger et al., who searched for brain areas related to social pain. In this study, participants played a virtual game, Cyberball, while functional magnetic resonance images were obtained. The Cyberball is a

virtual ball-tossing game created by Williams et al. (2000). It is a rather simple game where the participant throws the ball to the other two players, whom are thought of as "real" players in other laboratories connected via internet to carry out the experiment. But in fact, the participant is playing alone with the computer, which determines whether or not he will be excluded from the game, according to the aims of the investigator. This game may have three conditions. The first is an inclusion condition. In this condition, the participant plays with “others” and each player throw the ball a similar number of times. The second is an exclusion condition. Here, after an initial periodof playing, the other two players stop throwing the ball and start to only play with each other, excluding the participant. Finally, a third condition, considered a control condition, is similar to exclusion but the participant is informed that he cannot play because there was a technical problem. He can only watch the others playing. Eisenberger et al (2003) study, and others using this paradigm (e.g., Onoda et al., 2010; McQuaid et al., 2015; Pollatos et al., 2015) found that the Cyberball game induces social distress and changes participants’ psychophysiological responses (Kelly et al., 2012) as the participant is provoked by a group that he/she does not know and is not intimately or strongly connected.

Figure 6: Representation of Cyberball Inclusion and Exclusion condition as the participant sees it in the computer (from Eisenberger, 2012).



According to their predictions, Eisenberger et al. (2003) found that the social distress felt while excluded in the game was correlated to activation of the dorsal ACC and the AI. These areas are known to be key elements in the medial pain system which is associated with the processing of the distress and unpleasantness components of pain (Apkarian et al., 2005). Based on these results, the authors concluded that the dorsal ACC may operate as a "neuronal alarm system" signaling both social and physical threats. This supported an "overlap hypothesis" asserted by Eisenberger et al (2003; Eisenberger and Lieberman, 2004) and other authors: "(…) physical and social pain operate via common mechanisms. (…) Both types of pain share commons psychological correlates and physiological pathways." (MacDonald and Leary, 2005, p. 218). Accordingly, the study of social pain, as proposed by the authors (Eisenberger and Lieberman, 2004), cannot be understood merely as the emotional component of physical pain and suggests a different status when compared to other emotions that may modulate physical pain experience. They believed that the social and physical pain may be closely related and distinct from negative emotions that result from other aspects of human life (Eisenberger, 2015).

In social pain, theorists view the affective component of pain to be more relevant for experiencing the negative social experiences (Eisenberger, 2012). Yet, later studies tried to go further on the research of the similarities between these two types of experiences of suffering and hypothesized that more common brain regions could be found if the social distress induced was higher than the induced using Cyberball (Kross et al., 2011). Alternatively, Kross et al. (2011) studied relationship breakups, because they were more personal and intense. They recruited participants who were recently abandoned and exposed them to photos of their ex-partner, contrasted with photos of a close friend. The brain regions activated were then compared with regions involved in a heat pain contrasted with warm stimulation. Using this new paradigm they found that the sensory component of pain usually correlated to physical pain, specifically the secondary somatosensory cortex was also activated in social distress events. These findings contrasted with the neural correlates of bereavement which have not found the recruitment of the sensory component of physical pain (Gündel et al., 2003; O'Connor et al., 2008), but this has been interpreted as resulting from the absence of devaluation of self in bereavement. They argued that in romantic breakup, the subject suffers social

distress not only because he has lost a meaningful relationship, but also because his self was devaluated (Eisenberger, 2012).

Nevertheless, enthusiasm regarding the search for similarities between physical and social pain has been challenged recently. In fact, several objections may be done when comparing social distress and physical pain experiences based only in neuroimage findings. Although both events may induce great suffering and be highly relevant for human well-being and survival, they are quite different experiences (Iannetti et al., 2011). Activations of the ACC and AI are found in a wide range of emotional situations including dance, time perception, conscious of the heart beat, etc. (Craig, 2009), and the same is true for almost all of the areas of the "pain matrix", which may be activated in many sensory modalities, ranging from auditory, visual and somatosensory processing, thus indicating that all of these tasks involving cognitive multimodal relevant stimuli may involve similar activations (Iannetti and Mouraux, 2011).

A recent systematic review of neuroimaging studies of brain areas activated when using Cyberball or reliving breakups tasks, showed that the brain activations may not be in the same areas as those found in physical pain (Cacioppo et al., 2013; Woo et al., 2014), contrary to claims of many authors of the social pain approach (Kross et al., 2011; Eisenberger et al. 2012; Eisenberger, 2015). In fact, neuronal activations under pain stimulation, as under any other cognitive or emotional event, always involve a wide range of neuronal areas. It is not accurate to think that there may be such specificity for social distress or physical pain, or for both types of experience. Although the physical pain and social distress share the dimension of "suffering", sharing emotional salience, they are not invoked by the same stimuli. Social rejection is not a sensory experience in the same way a physical stimulus is.

Despite the importance of these criticisms, the fact that the activated neural areas are not the same in both situations does not change the relevance of searching for links between these two experiences. The line of research described encouraged studies that used different approaches for relating social distress and physical pain in animals (Briand et al., 2015) and humans (Hsu et al., 2013; Bonenberger et al., 2015).

In the later years, increase body of knowledge explored the relation between opioids and social behavior. It has been described that the opioid system, in addition to it's well-established key role in pain, is also activated under social distress events in physical pain brain regions, as ventral striatum, amygdala, thalamus and PAG (Hsu et al., 2013) and may contribute to decreasing social distress (Bershad et al., 2015). Susceptibility to social distress events was associated with polymorphisms in opioid receptor genes in animals (Briand et al., 2015) and humans (Way et al. 2010; Bonenberger et al., 2015).

Social distress has also been related to increased risk of inflammation (Hughes et al., 2014; Yang et al., 2014) and of inflammatory cytokines (e.g., TNF-alpha and IL-6) (Chiang et al., 2012; Rohleder, 2014). On the other hand, exposing individuals to inflammatory challenges increases depressive mood, social disconnection feelings (Eisenberger et al., 2010) and decrease performance on social cognitive tasks (Moieni et al., 2015a). Lately, it has also been described that this increase in social disconnection due to inflammatory challenge may be specific to females because of the increased vulnerability in women for suffering depression and chronic pain conditions (Moieni et al 2015b). Overall, these promising lines of research suggest possible molecular mediators that will be investigated in order to understand how social distress experiences may make individuals prone to be particularly sensitive to physical pain.

3.2 Social distress and pain

Another important question regarding the links between social distress and physical pain is if, and how, social distress modulates physical pain. In a first study (Eisenberger et al., 2006) conducted with this aim it was found that individuals who felt more social distress in the exclusion condition of Cyberball had a lower baseline pain threshold to thermal stimuli. In addition, it was also found that individuals more sensitive to the exclusion condition also felt heat painful stimuli applied during the game as more unpleasant. This study was based on the notion that social distress manipulation would have its impact on the cognitive-affective component of pain. As such, pain

unpleasantness was measured, but pain intensity was not. Yet, the results suggested that the relation between physical and social sensitivity may be bidirectional.

Interestingly, another study, using pressure pain instead of phasic heat pain, and using a different social distress paradigm found opposite results. DeWall and Baumeister (2006) use a false feedback from a personality questionnaire in order to induce social distress (Tweenge et al. 2001; DeWall and Baumeister, 2006). In this paradigm, participants are informed that, based on their answers to a questionnaire that they previously filled, it is possible to make predictions about their future. Accordingly, they are informed that it can be predicted that he will have many relational problems in the future and will end lonely in the future. Contrary to what was found in the Cyberball study (Eisenberger et al., 2006), the participants that receive the future lonely prediction increased pain pressure tolerance time and threshold after the feedback. These findings were interpreted as revealing a "numbness reaction". It was argued that anticipation of future rejection lead to a response of "numbness" in order to avoid higher suffering in the short-term, just as extreme physical pain can cause shock reactions with momentary analgesia (DeWall and Baumeister, 2006).

Due to these opposite findings, a later study tried to directly test the impact of the two social distress paradigms (Cyberball and future lonely) in the cold pressor test (Bernstein and Claypool, 2012). It was found that pain tolerance increased after the Exclusion condition of Cyberball and decreased after the future lonely feedback. The results were interpreted in accordance to a severity hypothesis: Cyberball may be a less severe "social injury", leading to hypersensitivity and future-life exclusion - a more severe, leading to numbness. However, in this study the impact of the paradigm on each participant was not assessed, and it is unknown if those more distressed felt less or more pain in each condition. Another possible explanation for the results might be related to the complex interactions of stress and pain. As already mentioned, it is known that stress may result in analgesia or hyperalgesia (Vidal and Jacob, 1986; Jørum, 1988). Animal studies have suggested that when there is lack of information to guide the response, the event induces higher arousal resulting in hyperalgesia. This may occur in the Cyberball game. Being excluded in Cyberball might be an odd situation, since the participant does not know the other players or the reason for being excluded. Nevertheless, there is

evidence that it is a stressful situation because it significantly induces altered physiological responses (Kelly et al., 2012; Bass et al., 2014; Iffland et al., 2014). It may be expectable that individuals feel high stress and higher arousal in Cyberball than in the future lonely paradigm, where although the prediction is bad, there is a prediction.

3.3 Induction of social distress in laboratory settings

Social pain is relatively easy to induce in laboratory setting and different methods to induce it are currently in use. One of the classical methods to induce social distress was the use of "Trier Social Stress Test". In this method, the participant makes arithmetic tasks and a free speech in front of a rejecting audience (Kirschbaum et al., 1993). This approach has been used in neuroendocrine studies, and it is a well established paradigm (Campbell and Ehlert, 2012; Allen et al., 2014; Frisch et al., 2015). In other studies, mostly using neuroimaging paradigms, exposing bereaved individuals to photos or memories of their deceased person (Gündel et al., 2003; Kersting et al., 2009) or exposing subjects that are going through relationship breakups to photos or memories of these experiences (Kross et al., 2007; Kross et al., 2012) have also been studied. As already described, the future lonely paradigm has already been used in studies of physical pain (DeWall and Baumeister, 2006).

Nevertheless, one of the most frequently used methods is the already described "Cyberball" paradigm (Williams et al., 2000). Cyberball was developed by Williams et al. (2000) for testing his "Need Threat Theory". In this theory it was proposed that ostracism, "the act of ignoring and exclusion" (Williams et al., 2000, p. 748) threats psychological needs of belongingness, self-esteem, meaningful existence and control. In the first large-cohort study using this tool Williams et al. (2000) found that exclusion from this game generated social distress asking participants to fill a questionnaire with subscales measuring each of these needs. This game was then adopted by many research teams with different aims (studying peer relationships, group processes, etc) and was the tool of the influential Eisenberger et al. (2003) study where it was shown that social and physical pain could have similar neuroanatomic substrates.

Cyberball has been used in several theoretical realms, for example, on child and adolescent development (e.g. White et al., 2013; Howard et al., 2014; van Noordt et al., 2015), on several personality disorders and behavioral disorders (e.g. Geniole et al., 2011; Gutz et al., 2015; Westermann et al., 2015). It has been used in real settings, subjected to manipulation of the variables involved (e.g. including real persons in the lab while playing the game, Weschke and Niedeggen, 2013) and using different populations (e.g. adolescents or clinical samples, as in studying autism spectrum disorders, e.g., Bungert et al., 2015; Sebastian et al., 2010).

There is evidence showing that the exclusion condition may induce altered physiological responses (Kelly et al., 2012; Iffland et al. 2014), a blunted cortisol response (Bass et al., 2014) and that it may be associated with adrenocorticotropic hormone changes in a subsequent public speaking stress in women (Weik et al., 2010; Weik et al., 2013) and higher progesterone levels (Seidel et al., 2013). Interestingly, the neuroendocrine and psychophysiological correlates of Exclusion condition in Cyberball are often not correlated do to subjective distress ratings (Seidel et al., 2013) suggesting that individuals may not be conscious of their stressful reaction. Recently it has been proposed that these reactions to Cyberball may be related to oxytocin receptor gene polymorphism (McQuaid et al., 2015) and that the neuroendocrine responses may be gender specific (Weik et al., 2010; Seidel et al., 2013).

Comparing the sensitivity to pain in social distress events may also depend on many individual differences. MacDonald (2008) found that the impact of social distress in the modulation of physical pain may depend on attachment style and Riva et al. (2014) showed that individuals sensitive to physical pain may also be to social distress, but these are different constructs. Recent studies on Borderline Personality Disorder corroborate this perspective (Bungert et al., 2015).

Chapter 4

4. Studies' aims and hypotheses

In the last decades, growing body of evidence highlight the relevance of social dimensions to pain experience, however, it is still under debate how these concepts are related. The aim of the two studies conducted within the framework of this thesis was to further investigate the relationships between social and physical pain experiences in healthy and chronic pain patients.

The first study aims were:

(1) To assess the relationship between social distress and pain sensitivity in healthy volunteers.

(2) To assess the effects of social distress on pain experience in healthy volunteers.

(3) To investigate if the relations between the social distress and pain experience is related to the individual differences such as attachment style and psychological disorders.

Our hypotheses were that:

(1) Individuals more sensitive to physical pain would also be more sensitive to social distress

(2) Social distress manipulation will modulate pain experience

(3) Individual differences, particularly, attachment style would affect relation between social distress and physical pain

The second study was aimed to extend the findings from healthy volunteers study and test the impact of social distress manipulation on pain in different chronic pain conditions. Two conditions were investigated: FM, which has been clearly related to

central sensitization mechanism and only recently has been provided evidence regarding peripheral process, and RA, where the peripheral mechanisms have been fully described, but only recently those related to central sensitization have been clearly recognized.

The second study aim was:

(1) To assess if social distress manipulation can differently modulate pain in different chronic pain conditions

Our hypothesis was:

(1) FM patients would demonstrate altered pain inhibition in response to social manipulation, compared to positive (RA) and negative (healthy) controls

Chapter 5

5. First Study – Healthy participants

This study was reported in: Canaipa, R., Treister, R., Moreira, J.M., & Caldas A.C. (2016) Feeling hurt: pain sensitivity is correlated with and modulated by social rejection. *Clinical Journal of Pain, 32*(1), 14-19.

5.1 Abstract

Objectives: Social distress, resulting from loss or threat to social relationships, shares similar psychological and neuronal processes with physical pain. Recent evidence demonstrated that social distress may have an impact on pain. The current study aimed to further assess the relationship between these two phenomena.

Methods: Sixty healthy participants were randomly assigned to inclusion, non-inclusion or exclusion conditions of Cyberball, a virtual ball tossing game used to induce social distress. Pain and unpleasantness in response to noxious electrical stimuli were assessed before and after Cyberball manipulation. Psychological characteristics were evaluated by the Experiences in Close Relationships Questionnaire and the neuroticism scale of Big Five Inventory.

Results: Significant correlations were found between social distress and baseline unpleasantness thresholds ($p=0.012$). Participants who perceived the Cyberball task as more distressing demonstrated lower unpleasantness thresholds. Post Cyberball manipulation, perceived pain intensity (3.1 ± 0.8), but not unpleasantness (3.9 ± 0.3), was significantly ($p=0.001$) lower in the inclusion condition compared to pre-Cyberball pain (4). No associations were found between the psychological characteristic and the effects of Cyberball on pain or unpleasantness.

Discussion: The current study results indicate that participant's baseline sensitivity to unpleasantness is related to their responsiveness to social distress and that physical pain may be modulated by social events. Further studies are needed to clarify the clinical relevance of these results.

Key words: Pain, social distress, social rejection, Cyberball

5.2 Introduction

The role of pain in organisms' survival is well known, yet human survival, as in many other species, also depends on social relations (Panksepp, 1998). As such, the risk of losing social relationships can be as serious as actual physical threats (Eisenberger and Lieberman, 2004; Macdonald and Leary, 2005). As social attachment theory proposes (Bowlby, 1973), social rejection events, involving threats to social bonds, may be particularly significant to mental (Monroe et al., 1999) and physical health (Mikulincer and Florian, 1998). Accordingly, the term 'social pain' is defined as pain resulting from loss, threat, or damage to social relationships (Eisenberger et al., 2003).

Social distress can be effectively induced in a laboratory setting with a variety of available techniques. For example, in the "Trier Social Stress Test", participants complete arithmetic tasks and deliver a free speech in front of a rejecting audience (Kirschbaum et al., 1993). In the future life exclusion paradigm, participants complete a personality test and receive a false feedback from the experimenter: They are informed that based on test results, it is expectable that they will end up lonely in life (Twenge et al., 2001; DeWall and Baumeister, 2006). Other studies have used real life personal bereavement situations, in which strong affective reactions are induced by exposing participants to pictures of a lost loved one (a deceased or an ex-partner) (Gündel et al., 2003; Kross et al., 2007; Kersting et al., 2009; Kross et al., 2011).

"Cyberball" is another frequently used method (Williams et al., 2000) in which participants believe they are playing a computerized virtual ball tossing game with other real participants. Social distress is induced, depending on the extent of subject inclusion by the "other players" in the game. Social distress is measured by the William's social

distress questionnaire which assesses the impact of playing the game on 4 domains of psychological needs: belonging, self-esteem, meaningful existence and control. In addition to these sub-scales, a total social distress score is calculated. Using the Cyberball paradigm, Eisenberger and colleagues elegantly demonstrated the bi-directional interactions of pain and social distress (Eisenberger et al., 2006). In their study, the unpleasantness of pain stimuli was assessed at baseline and during the Cyberball paradigm. They demonstrated that those who perceived the stimuli as more unpleasant at baseline (i.e. demonstrated lower pain unpleasantness thresholds), were more sensitive to the rejection manipulation (i.e. felt more distressed during the rejection episodes). On the other hand, pain unpleasantness was affected by social distress: subjects who were more sensitive to the social manipulation also perceived higher unpleasantness in response to painful stimuli during the Cyberball manipulation. However, other studies have demonstrated an opposite relation between social distress and pain: DeWall and Baumeister (2006) found increases in pressure pain thresholds and pain tolerance following social distress induced by the future life exclusion paradigm.

In sum, the present study aimed to further assess the relations between subjects' sensitivity to physical pain and their susceptibility to social distress. We hypothesized that: (1) individuals who are more sensitive to physical pain would also be more sensitive to social exclusion situations and that (2) induction of social distress would affect subjects' pain sensitivity. Previous studies have shown the role of attachments style in rejection manipulations (MacDonald, 2008) and sensitivity to social distress (Karremans et al., 2011; DeWall et al., 2012), thus, we assessed if attachment style affects relation between social distress and physical pain.

5.3 Material and Methods

5.3.1 Participants

Sixty participants were recruited from the undergraduate degree program of the Faculty of Psychology at the University of Lisbon. Participants received course credits for their participation.

5.3.2 Tools

5.3.2.1 Experimental apparatus

Pain was induced by a bipolar felt pad electrode (Digitimer, Hertfordshire, England) placed on the left arm, near the wrist (posterior). The electrode, filled with conductive gel, was connected via extension cable to a constant current stimulator (Digitimer, model DS7A; Hertfordshire, England) in the experimenter room. The stimulator had a Bayonet Neill-Concelman connector (BNC) trigger input socket that allowed the connection of a synchronizer (Plux Wireless Biosignals, SA, Lisbon, Portugal). The experimenter's computer "triggered" the stimulus in the form of a transistor-transistor logic (TTL) trigger pulse, allowing the DS7A to be triggered externally.

5.3.2.2 Social distress manipulation and assessment

The Cyberball procedure was used to induce social distress as demonstrated in Eisenberger et al (2003). Cyberball is a virtual ball tossing game developed by Williams et al. (2000) to manipulate feelings of social rejection. In this procedure, subjects believe they are playing with other participants sitting at other computers else where and connected via an internet network. In fact, however, the other two players are simulated by the software. The Cyberball manipulation comprises three study conditions: (1) In the inclusion condition, participants play with the other 'players' and no social distress occurs. There are two exclusion conditions (2) In the overtly excluded condition, at first the other 'players' throw the ball to the participant, but then they start tossing the ball only between the two of them and the participant never again receives the ball. (3) In the non-inclusion condition the same situation occurs, but the participant is informed that the other participants are unable to pass the ball to him/her due to technical problems.

The psychological impact of the Cyberball was assessed according to Williams et al. (2000), with Belonging (e.g. "I felt disconnected"), Self-esteem (e.g. "I felt liked"), Meaningful Existence (e.g. "I felt meaningless"), Control (e.g. "I felt I had control over the course of the game") subscales, with each item answered on a 5-point scale ranging from

"Not at all" to "Extremely". The total score is obtained from the average of subscales scores. This measure was used according to previous studies (Eisenberger et al., 2003; Eisenberger et al., 2006): Higher ratings indicate that the participants felt their psychological needs threatened to a greater degree and, as such, felt more socially distressed after the game. At the end of the study, subjects were directly asked whether they believed that they were playing with players from other labs.

5.3.2.3 Pain Stimulation Pre-Cyberball

Familiarization trial

Participants were initially exposed to three stimuli, to familiarize them with the procedure and with the pain and unpleasantness ratings. The participant rated each stimuli by moving sliders controlled by the mouse in two computerized visual analogue scales (Co-VAS): pain intensity and pain unpleasantness. The scales aimed to assess sensory and emotional components of pain (respectively). On the first slider, they rated the perceived pain, ranging from 0, corresponding to "not painful at all" to 10, corresponding to "the worst pain one can imagine". On the second slider, they rated unpleasantness, ranging from 0, "not unpleasant at all" to 10, "the most unpleasant one can imagine".

Calibration

An ascending sequence, started with an intensity of 40 mA and augmented in 20 mA steps, was administered to individually adjust stimulation intensity. Stimuli duration was 0.2 ms with inter-stimuli intervals randomly distributed between 15 and 20 seconds. The sequence was terminated when participants rated their pain as 6. The lowest stimulus intensity that was rated as painful was considered as the pain (or unpleasantness) threshold.

A second stimulation sequence was constructed based on the ascending sequence results. This was an 11-stimuli, random sequence calibrated so as to deliver equally-spaced intensity stimuli between the threshold (intensity rated as 1) and the intensity rated as 6. These intensities were extrapolated for each participant to correspond a 0 to

10 scale with 11 stimulation intensities using the following formula- threshold stimulation intensity + 0.1*(pain 6 stimulation intensity - threshold stimulation intensity) (this is an example for calculating intensity of 1, 0.2 instead of 0.1 was used to calculate 'pain 2' intensity and so forth). Participant's responses to the second stimulation sequence were used for constructing the post Cyberball stimulation sequence.

5.3.2.4 Pain stimulation Post-Cyberball

At the end of the game, participants received 3 stimuli calibrated for targeting a pain intensity of 4. This was done by using a simple linear regression carried out for each participant individually immediately after the 11-stimuli sequence, yielding the required stimulus intensity for the next stage of the experimental procedure. The regression formula used was as follows: = (4-a)/b (***a*** is the *mean* of the participants' intensities ratings in response to the 11 stimuli minus ***b*** multiplied by the mean of the intensities, ***b*** is the mean of the $\Delta x \Delta y$ divided by Δx^2). These three stimuli had the same duration and interval as in the previous sequence. In response to each stimulus, participants rated pain intensity and unpleasantness by using the Co-VAS. Post Cyberball stimulation pain and unpleasantness were calculated as the mean response to these three stimuli.

5.3.3 Questionnaires

In addition to participant demographic information, the Experiences in Close Relationships questionnaire (ECR) and the Portuguese version of the Big Five Inventory (BFI) questionnaires were completed prior to the Cyberball manipulation.

Before the Cyberball manipulation, close relationship style was assessed by using the Experiences in Close Relationships questionnaire (ECR) (Brennan et al., 1998), which measures the two fundamental dimensions in adult attachment style: Preoccupation and Avoidance. It contains 36 items, rated on a 7-point scale, ranging from 1 "strongly disagree" to 7 "strongly agree", and a central point of 4 "neutral/mix". The Portuguese

version of this questionnaire was developed by Moreira et al. (2006) and has been shown to have adequate psychometric properties.

At the end of the procedure, subjects completed the neuroticism scale of the Portuguese version of the Big Five Inventory (BFI) (John and Srivastava, 1999) to confirm that the impact of the Cyberball manipulation was not confounded by an individual tendency to appraise situations as threatening. This scale consisted of 7 items rated on a 5-point scale ranging from 1 for “strongly disagree” to 5 for “strongly agree”. The Portuguese version was developed and validated by Moreira (2002).

5.3.4 Procedure

The study was approved by the Ethics and Deontology Commission of the Faculty of Psychology of University of Lisbon. As a first step of the study, on the morning of the experiment, participants completed online the demographic and Pre-Cyberball questionnaires sent via e-mail. Later on the same day, participants came to the laboratory for the second part of the study. Informed consent was obtained from all subjects prior to the beginning of each part of the study. Participants were told that the study aim was to assess the impact of working with video screens on the perception of pain. The participants were seated in a small room in front of a computer screen with the electrode attached to their wrist. This room was contiguous to the experimenter room but was separated by two doors so the experimenter could not see or interact with subjects.

Following the pre-Cyberball pain stimulation, each participant was randomly assigned to one of the three Cyberball conditions. Assignment was automatically done by the computer so that the experimenter did not know to which study condition subjects were assigned to until the beginning of the Cyberball game. In the non-inclusion condition, the experimenter entered the participants’ room to inform about ‘technical problems’ and ask the participant to continue concentrating on the game. At the end of the game, post-Cyberball pain stimulation was administered and questionnaires were completed. After completion of the entire procedure, subjects were fully informed about the actual aims of the study and the rejection manipulation.

5.3.5 Statistical analysis

Analyses were conducted by the SPSS for Windows Version 19 statistical package (SPSS, Inc., Chicago, IL) (IBM, 2010). Chi Square and analysis of variance (ANOVA) tests were used to assess differences in demographic characteristics between study groups. ANOVA was utilized to assess differences between study conditions in baseline pain and unpleasantness, psychological characteristics, social distress and post-Cyberball pain and unpleasantness. Pearson's correlation was used to study relations between post-Cyberball pain and unpleasantness, social distress and psychological characteristics. The one sample t-test was utilized to assess differences between post-Cyberball pain intensity and unpleasantness and the predicted value of 4. Values are presented as means and standard deviations (SD). Results of all analyses were considered significant at the $p < 0.05$ level.

5.4 Results

5.4.1 Subjects' characteristics and manipulation check

Of the sixty subjects recruited to the study, 21 were assigned to the exclusion condition, 20 to the non-inclusion and 19 to the inclusion condition. In response to the question "did you believe that you were playing online with real participants", 9 subjects answered negatively, and were excluded from further analyses. These 9 participants were from the Inclusion condition (n=2), the non-inclusion condition (n=1) and the exclusion condition (n=6). Therefore, the final cohort consisted of 51 participants (n=15 in the exclusion condition; n=19 in the non-inclusion; n=17 in the inclusion), 43 females and 8 males with mean age of 20.6 (SD = 3.5) years. Subjects' gender (Chi Square, $p = 0.093$), age (ANOVA, $p = 0.211$) and socio-economic status (ANOVA, $p = 0.505$) did not significantly differ among Cyberball conditions.

Table 2: Participants' demographic characteristics.

	Entire Cohort		Included		Non-Included		Excluded	
	M	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**
Age	20.59	3.49	21.53	4.90	20.58	3.13	19.53	1.13
	fr	**%**	**fr**	**%**	**fr**	**%**	**fr**	**%**
Gender								
Male	8	15.70	2	11.80	5	26.30	1	6.70
Female	43	84.30	15	88.20	14	73.70	14	93.30
Education								
9 grade	1	2.00	0	0	0	0	1	6.70
12 grade	41	80.40	12	70.60	15	78.90	14	93.30
Graduation	9	17.60	5	29.40	4	21.10	0	0
Socio-economic status								
Low	1	2.00	0	0	1	5.30	0	0
Mediu-low	15	29.40	4	23.50	4	21.10	7	46.70
Médium	31	60.80	12	70.60	12	63.20	7	46.70
Medium-high	4	7.80	1	5.90	2	10.50	1	6.7

5.4.2 Baseline pain and unpleasantness thresholds

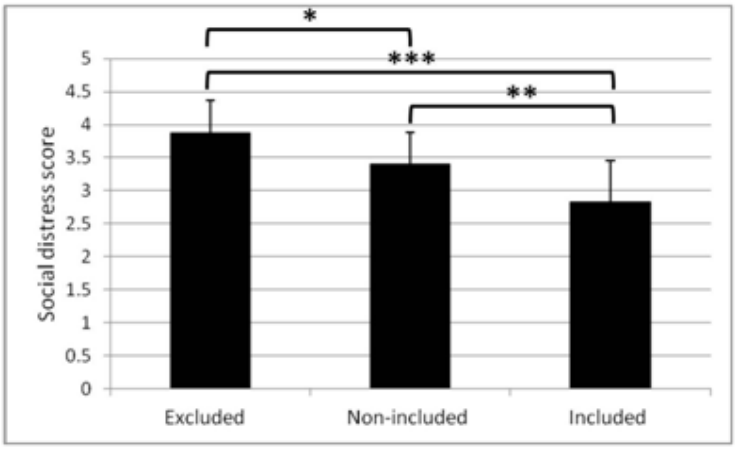
Mean (±SD) intensities needed to induce pain and unpleasantness thresholds were 96.7±64.4 mA (range between 20 to 320 mA) and 77.6±47.5 mA (20-220), respectively. ANOVA test revealed no significant differences in pain and unpleasantness thresholds between Cyberball conditions.

5.4.3 Social distress

Mean (±Std) social distress scores after the Cyberball game were 3.35±0.7 (minimum 1.9 maximum 4.6). One-Way ANOVA revealed significant differences in social distress after the Cyberball game among Cyberball conditions ($F=14.3$, $p<0.001$). Specifically, social distress scores were significantly higher in the excluded condition (mean±SD, 3.9±0.49) than in the non-included (3.4±0.49; $p=0.016$) and the included condition (2.8±0.62; $p<0.001$). Social distress mean scores in the non-included condition

were significantly higher than in the included condition (p=0.003; Figure 1). Descriptive statistics of the two attachment style subscales (avoidance and preoccupation) and the neuroticism total score are described in table 1. ANOVA test revealed no significant differences among Cyberball conditions in any of these measures.

Figure 7: Social distress after Cyberball in the 3 game conditions.



*P<0.05; **P<0.01; ***P<0.001

Table 3: Participants' scores in the Experiences in Close Relationships Questionnaire and Neuroticism Scale of Big Five Inventory.

	Mean ± SD	Minimum	Maximum
ECR Avoidance	70.6±15.3	38	98
ECR Preoccupation	12.6±5.3	4	26
BFI Neuroticism	21.8±4.6	8	30

ECR- Experiences in Close Relationships Experiences, BFI- Inventory Big Five.

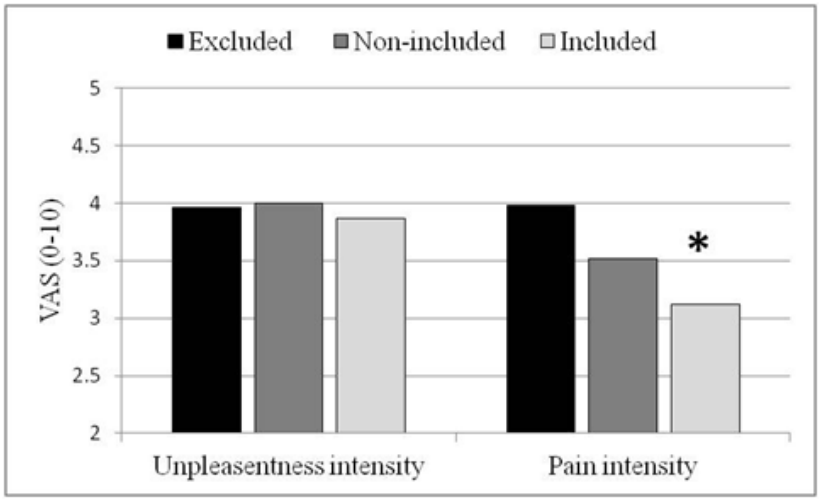
5.4.4 Relations between baseline pain, unpleasantness thresholds and social distress

Our first hypothesis was partially confirmed, as demonstrated by the significant positive correlation between social distress and unpleasantness thresholds ($r = -0.358$, $p = 0.012$) but not with pain thresholds ($r = 0.226$, $p = 0.119$). Psychological characteristics were not significantly correlated with baseline pain or unpleasantness thresholds or with social distress.

5.4.5 Post-Cyberball pain and unpleasantness

Mean (±Std) of the perceived intensities of the pain and unpleasantness after Cyberball conditions were 3.51±1.1 and 3.95±1.6, respectively. According to our second hypothesis, pain intensity in the included condition (3.1±0.8) was significantly lower than 4 (One sample t-test, $p = 0.001$), while unpleasantness (3.9±0.3) did not significantly differ from 4 ($p=0.677$, Figure 2). In the non-inclusion condition, pain (3.5±1.3) and unpleasantness (4±1.7) were not significantly different from 4 ($p=0.188$ and $p=1$, respectively), as well as in the excluded condition (pain 4±1.1; unpleasantness 4±1.7).

Figure 8: Pain and unpleasantness intensity after Cyberball in the 3 game conditions.



*P=0.001, one sample t-test, test value=4.

5.5 Discussion

The current study was aimed to shed more light on the complex relations between social distress and pain sensitivity. Our hypotheses were that (1) individuals who are more sensitive to physical pain would be more sensitive to social exclusion situations and (2) induction of social distress would affect subjects' pain sensitivity. Both hypotheses were partly confirmed: At baseline, the intensity needed to reach unpleasantness thresholds correlated with social distress. Following induction of social distress, subjects in the inclusion condition (low social distress) perceived the painful stimuli as less painful than predicted.

Our first key finding was that social distress after Cyberball correlated with baseline unpleasantness thresholds, but not with baseline pain thresholds. Similarly, Eisenberger et al. (2006) used thermal stimuli and found correlations between social distress induced by Cyberball and baseline unpleasantness sensitivity. However, Eisenberger et al. (2006) did not measure pain intensity. These relations between social distress and pain unpleasantness line up with imaging studies which demonstrated that social distress is linked to brain areas in which pain's emotional-cognitive dimensions are processed (Eisenberger et al., 2003; Eisenberger, 2012). In any case, recent studies demonstrated mixed results (Cacioppo et al., 2013; Woo et al., 2014) and therefore the extent to which pain and social distress share neurocognitive processes is yet to be determined.

Our second finding highlights the effect of social distress on pain. Specifically, following Cyberball, and in response to noxious electrical stimulation, subjects who reported lower social distress (inclusion condition) perceived the stimuli as less painful, but not less unpleasant. In contrast, Eisenberger et al. (2006) have shown that during the social rejection conditions, social distress was positively correlated with unpleasantness ratings. These differences may be the result of differences between studies methodologies. First, in Eisenberger et al. (2006), unpleasantness assessment was based on a 21 point scale, ranging from 0 "neutral" to 20 "unbearable" (with '10' representing the threshold) while pain intensity was not assessed at all. Second, painful stimuli in Eisenberger et al. (2006) were delivered during the Cyberball condition, while in the

current study stimulation was performed after the social distress intervention. Third, time of social distress assessment also differed between studies: while Eisenberger et al. (2006) assessed social distress after subjects were exposed to the painful stimulation, social distress in the current study was assessed immediately after Cyberball, prior to the painful stimulation. Lastly, stimulus modalities also differed (electrical vs. thermal).

Interestingly, it has been shown that social distress induced by a different paradigm results in analgesia, rather than hyperalgesia: DeWall and Baumeister (2006) demonstrated a "numbness reaction" following induction of social distress by using the future life exclusion paradigm. Specifically, increases in pressure pain thresholds and pain tolerance were observed following the manipulation. The authors suggested that anticipation of future rejection lead to a response of "numbness" in order to avoid higher suffering. A later study directly compared the impact of social distress induced by the Cyberball paradigm with the future life exclusion paradigm (Bernstein and Claypool, 2012). While hyperalgesia (diminished threshold and tolerance to cold stimuli) was found in the excluded group following the Cyberball paradigm, an opposite effect of analgesia was induced by the future life exclusion paradigm. The authors interpreted these results in accordance to a severity hypothesis: Cyberball may be a less severe "social injury", leading to hypersensitivity, while future-life exclusion might be more severe, leading to hyposensitivity.

Another possible explanation might be related to the complex interactions between stress and pain. As a known fact, stress may result in analgesia or hyperalgesia (Vidal and Jacob, 1986; Jørum, 1988). Evidence from animal studies have demonstrated that in case there is a lack of information to guide a response, as may occur in the Cyberball game, arousal may induce hyperalgesia. Indeed, being excluded in Cyberball induces higher skin conductance level, a measure of arousal, compared to inclusion (Kelly et al., 2012).

Notably, our results suggest that social rejection does not increase pain sensitivity or unpleasantness but, rather, that social inclusion helps to reduce pain intensity. One might argue that the observed effects are actually due to social support, rather than social distress. However, the fact that social distress was induced in all subjects (there

were no ‘0’ scores in social distress scale), implies that this is probably not the case. Other explanations might be related to our specific methodology (i.e. our painful stimuli protocol). This issue deserves further investigation.

No relations between social distress and any of the studied psychological measures were found in the current study. In contrast, MacDonald (2008) studied the effect of social distress induced by two paradigms, Cyberball and recalling past exclusion experiences, on pain. They concluded that subject’s attachment styles might have an important role in the effects of social distress on pain. Similarly to Eisenberger et al. (2006) results, we found no relations between neuroticism and social distress or pain in our study. This may suggest that stress induced by Cyberball is specific and cannot be explained by a general tendency to appraise events as threatening. In contrast, Riva et al., (2014) have recently demonstrated that fear of social threat modulates sensitivity to social distress. Future studies are warranted to assess the effects of psychological characteristics on social distress and pain.

Several limitations of the current study deserve considerations: (1) during threshold assessment, some subjects rated ‘2’ (on the 0-10 scale) in response to the first stimulus that was perceived as painful (threshold). This implies that we should have used smaller increases in stimulus intensities between consecutive stimuli during threshold assessments. (2) The number of participants excluded due to their disbelief in the Cyberball game differed among conditions, something that may have undermined random assignment. (3) Our pain stimulation protocol implied different pain intensities pre- and post-manipulation. This limits our ability to easily understand manipulation effects. Lastly, our relatively small sample size may have led to low power and to the inability to detect significant effects.

The current study, together with previous studies, indicates that sensitivity to pain relate to sensitivity to social distress. The effects of social distress on pain are particularly relevant in those chronic pain conditions that are known to be “stress related”. A better understanding of the impact of social events on chronic pain patients can help healthcare providers and patients to better diagnose and deal with the painful conditions. Future

studies aimed at throwing light into mechanisms underlying these relationships will hopefully help in the development of new treatment approaches.

Chapter 6

6. Second Study – Fibromyalgia patients

This study is currently under review as: Canaipa, R., Castro-Caldas, A., Moreira, J.M., Pimentel-Santos, F., Branco, J.C., & Treister, R. Impaired pain modulation in Fibromyalgia patients in response to social distress manipulation (*Clinical Journal of Pain*).

6.1 Abstract

Background: Fibromyalgia (FM), a chronic pain condition, is associated with abnormalities in the descending pain modulatory system. Among other factors, a growing body of evidence has shown that social distress modulates pain sensitivity. The current study aimed to assess the effects of social distress manipulation on pain in FM patients compared to positive (Rheumatoid Arthritis, RA) and negative (pain-free) controls.

Methods: FM, RA patients and Healthy Controls (HC) were recruited. Demographic, medical and psychological characteristics were collected. Each participant was exposed to three study conditions in a random order: The Inclusion (positive social effects) and Exclusion (negative social effects) conditions of Cyberball, a game that manipulates social distress, and a control condition. Pain sensitivity in response to nociceptive electrical and thermal stimuli was assessed before and during each study condition.

Results: In response to electrical stimuli, pain decreased in both the Inclusion (pain=-13.71±45.28 and unpleasantness=-20.78±28.7) and Exclusion conditions (pain=-13.66±33.31 and unpleasantness=-18.04±30.89) in HC and RA (Inclusion: pain=-7.50±34.54; unpleasantness=-5.60±38.04; Exclusion: pain=-3.36±37.57; unpleasantness=-4.40±38.04) groups, while in the FM group, Inclusion condition significantly (p=0.019) increased pain (Inclusion: pain=7.50±26.04; unpleasantness=2.86±31.98; Exclusion: pain=-

9.04±23.56; unpleasantness=-14.34±21.13). Social manipulation (Inclusion or Exclusion) did not affect pain sensitivity as measured in response to thermal stimulation.

Conclusions: These results are in line with previous studies demonstrating altered pain inhibition by positive emotions in FM patients and suggest that unlike HC or other non-"stress-related" chronic pain conditions, being socially included may increase pain perception in FM patients. Possible underlying mechanisms and clinical relevance are discussed.

6.2 Introduction

FM is a common disabling chronic pain condition, which presents with widespread pain and fatigue as major symptoms. Sleep disturbances, morning stiffness, gastrointestinal disorders, cognitive deficits, depression and anxiety are also present (Williams and Clauw, 2009). Abnormalities in pain processing, such as hyperalgesia, temporal summation and allodynia have been extensively described (Vierck, 2006; Staud, 2007) and have been associated to impairment in the descending pain modulatory system (Kosec and Hansson, 1997; Julien et al., 2005; Rhudy et al 2013).

Descending pain modulation may result in either inhibitory (anti-nociceptive) or facilitatory (pro-nociceptive) effects mediated by descending Noradrenergic, Serotonergic and Dopaminergic tracks projecting to the spinal cord dorsal horn (Tracey and Mantyh, 2007; Benarroch, 2008; Treister et al., 2013). Descending modulation can be triggered peripherally (e.g. "pain inhibit pain", Conditioned Pain Modulation, CPM) or centrally (e.g. cognitive or emotional manipulations).

Cumulative evidence has shown abnormal pain modulation in FM patients. For example, FM patients demonstrate abnormal CPM (Ge et al., 2012; Paul-Savoie et al., 2012; Chalaye et al., 2014). In addition, deficits in pain modulation seem to be influenced by emotional manipulation among these patients (Kamping et al., 2013; Rhudy et al., 2013).

Social distress has been described as a real life situation that has shown to modulate physiological (Kemeny, 2009; Slavish et al., 2010) and behavioral pain-related

responses in laboratory settings (Einsenberger et al., 2006; Canaipa et al., 2016). It has been mostly studied using Cyberball, a paradigm based on a virtual ball tossing game, where participants believe they are playing with other real participants (Williams et al., 2000). In fact, they are playing with a pre-programmed computer that can enroll the participant into one of two conditions: A condition in which the participant is socially included and one in which he or she is excluded from the game. In healthy individuals, sensitivity to social distress induced by Cyberball is correlated with sensitivity to pain (Eisenberger et al., 2006). A recent study from our laboratory demonstrated that not only does social distress modulate pain, but social inclusion may actually reduce pain intensity (Canaipa et al., 2016). Clinically, it has been shown that increased loneliness and social burdens are associated with chronic pain conditions (Kool and Geenen, 2012).

The impact of social distress on pain sensitivity in FM has not yet been studied. To this end, the current study was aimed to investigate the modulatory role of social distress on pain sensitivity in FM, RA and HC individuals. The effect of Cyberball manipulation on pain and unpleasantness as measured in response to phasic (electrical) and tonic (cold) noxious stimuli were assessed. We hypothesized that FM patients will demonstrate altered pain inhibition under social manipulation.

6.3 Methods

6.3.1 Participants

Patients were recruited from Myos, The Portuguese Association of Fibromyalgia and Chronic Fatigue Syndrome and from the Rheumatology Department of the Centro Hospitalar de Lisboa Ocidental, Hospital Egas Moniz. HC were students and employees recruited from local universities. FM patients were diagnosed according to 1990 American College of Rheumatology (ACR) classification criteria and also met the recently proposed Wolfe et al. (2010) diagnostic criteria. RA patients were diagnosed according to 1987 ACR Criteria. They all had stable therapy doses 4 weeks prior to the study, were over 18 years of age, female, and capable of providing informed consent. Exclusion criteria

included current pregnancy or breastfeeding, any persistent or severe infection within 30 days of baseline, formal diagnosis of psychiatric conditions, history of rheumatic disease beyond the one specific of each group, any uncontrolled medical condition (e.g., uncontrolled diabetes mellitus, unstable ischemic heart disease), and history or signs of demyelinating disease.

6.3.2 Social distress manipulation

The Cyberball procedure was used to induce social distress as demonstrated in Eisenberger et al. (2006). Cyberball is a virtual ball tossing game developed by Williams et al. (2000) to manipulate feelings of social distress. In this procedure, participants believe they are playing with other players connected via the internet. However, the other players are actually simulated by a computer program. In the current study, two conditions of the Cyberball game were applied: (a) an Inclusion condition, in which participant plays with the other 'players' and no social distress is expected, (b) an overt Exclusion condition, in which the other 'players' throw the ball to the participant in the beginning, but then start to toss the ball between themselves, and the participant never receives the ball again. Each participant was enrolled to both Inclusion and Exclusion conditions. Each condition comprised 40 throws and took approximately 4 minutes. The psychological impact of the procedure was assessed immediately after each Cyberball condition, according to Williams et al. (2000), with Belonging, Self-Esteem, Meaningful Existence and Control subscales.

6.3.3 Experimental pain assessment

6.3.3.1 Electrical stimulation

Electrical pain was induced by a bipolar felt pad electrode (Digitimer, Hertfordshire, England) placed on the right arm, near the elbow. The electrode, filled with conductive gel, was connected via an extension cable to a constant current stimulator (Digitimer, model DS7A; Hertfordshire, England) in the experimenter's room. The stimulator had a Bayonet Neill-Concelman connector (BNC) trigger input socket that

allowed the connection to a synchronizer (Plux wireless biosignals, SA, Lisbon, Portugal). The experimenter's computer "triggered" the stimulus in the form of a transistor-transistor logic (TTL) trigger pulse, allowing the DS7A to be triggered externally.

Familiarization

The familiarization session consisted of stimuli applied in an ascending sequence. Each stimulus was rated verbally in terms of intensity of pain and unpleasantness on a Numerical Pain Scale (NPS), ranging from 0 to 10, where 0 corresponded to "not painful at all" or "not unpleasant at all" and 10 to the "worst pain one can imagine" or "the most unpleasant one can imagine". The stimulation began with 10 mA and increased in steps of 10 mA until the participant rated the pain intensity as 6. Each stimulus was 200 ms long and there was a 10-second interval between stimuli.

Stimulation before and during each study condition

The intensity used before and during each study condition was individually adjusted using linear regression, based on the reported intensities corresponding to the minimum (intensity at which the participant gave the first 1 in pain intensity) and the maximum (intensity at which the participant gave the first 6 in pain intensity) recorded at the familiarization session. Three stimuli aimed to induce a mean pain rating of 5 on the NPS were used. Stimuli were not identical: small increases in the 3 stimuli were included to account for habituation, which is prominent when electrical stimulation is used. The exact same stimuli were applied before and during the Cyberball and control conditions.

6.3.3.2 Cold stimulation

For the cold pain stimulation, participants were asked to place their left hand into an ice water bowl.

Familiarization

Participants entered the palm of their hand into the ice water and held it there for 20 seconds. Pain and unpleasantness rating (NPS0-10) were captured at 10s and 20s of stimulation.

Cold pressor test during each study condition

Participants immersed their left hand in the cold water bath and were instructed to keep it submerged for as long as they could (up to a safety limit of 3 minutes). When participants withdrew their hand from the water they rated their maximal pain and unpleasantness during immersion on the corresponding pain and unpleasantness NPS. Participants were instructed that they could pull their hand out of the ice water at any time during the test. Time to hand withdrawal was registered as cold pain tolerance.

6.3.4 Clinical assessment

6.3.4.1 Clinical Pain intensity

At the beginning of the study, prior to any stimulation, participants rated their current pain intensity on the NPS scale ranging from 0 for “no pain at all” to 10 “the most pain one can feel”.

6.3.4.2 Brief Pain Inventory (BPI)

The BPI is a pain self-report measure assessing pain in a multidimensional perspective (Cleeland and Ryan, 1994). It includes 15 items revolving on the existence of pain, its severity, location, therapeutics, and functional impact. The Portuguese version of the BPI revealed good psychometric properties (Azevedo et al., 2007).

6.3.4.3 Fibromyalgia Impact Questionnaire (FIQ)

The FIQ was used to assess the health problems related to FM and its impact on daily living (Burckhardt et al., 1991). It comprises information about function, overall impact, and symptoms. The Portuguese version of this questionnaire was developed by Rosado et al. (2006) and demonstrated good psychometric properties.

6.3.4.4 Health Assessment Questionnaire (HAQ)

The HAQ is a questionnaire specifically developed for Rheumatic patients, to assess quality of life and functional status (Fries et al., 1980). It was validated in Portuguese RA population (Santos et al., 1996).

6.3.4.5 Short Form Health Survey SF-36

The SF-36 measures participants' perception of general health (Ware and Sherbourne, 1992). It measures eight health domains. The Portuguese version of SF-36 revealed good psychometric properties (Pais-Ribeiro, 2005).

6.3.4.6 Hospital Depression and Anxiety Scale

The Hospital Depression and Anxiety Scale is a brief instrument commonly used to assess anxiety and depression in physically ill populations (Zigmond and Snaith, 1983). It includes two subscales, depression and anxiety. The Portuguese version of this instrument was considered adequate (MacIntyre et al., 1999).

6.3.4.7 Medication consumption

Participant's medication (and dosage) regimen was registered.

6.3.5 Procedure

The study was approved by the Ethics Committee of the Rheumatology Department of Centro Hospitalar de Lisboa Ocidental (CHLO), Hospital Egas Moniz. Informed consent was obtained from all subjects prior to the study. Participants were told that the aim of the study was to assess the impact of working with video screens on pain perception. Participants were seated in front of a computer screen and completed the questionnaires. Following the familiarization, each participant was randomly assigned to one out of six possible sequences of the three study conditions (two Cyberball conditions and control). Electrical stimulation was applied before and during each condition. Immediately after the end of electrical stimulation, while subjects were still actively playing Cyberball, the cold pressor test was conducted. At the end of each Cyberball condition, the Social distress questionnaire was completed. At the end of the experiment, subjects were asked if they believed they were playing Cyberball with real participants from other labs connected via the internet and were fully informed about the real aim of the study.

6.3.6 Statistical analysis

Analyses were conducted using SPSS for Windows Version 19 statistical package (SPSS, Inc., Chicago, IL) (IBM, 2010). A few of the pain measures were not normally distributed. Therefore, all analyses were non-parametric (Treister et al., 2015). Chi Square (in case of categorical variables) and Spearman correlations were conducted. The non-parametric Kruskal-Wallis test was used to compare outcomes between the three study groups and the Mann-Whitney test for post-hoc analysis. Wilcoxon tests were used in case of within-subjects analysis. P-values were regarded as significant when below .05.

For electrical pain, the effect of Cyberball on pain and unpleasantness were calculated as the difference between the ratings before the study condition and during the study condition (Inclusion, Exclusion and Control, separately). These values were transformed into percentage of change (delta of pain/rating before the condition)*100.

For cold pain, the difference between the control and the two Cyberball conditions (inclusion and exclusion) was calculated for each variable (tolerance, pain and unpleasantness). Each of these were then transformed into percentage of change (delta/ Control)*100.

6.4 Results

6.4.1 Subject characterization

Ninety female participants were recruited, 33 diagnosed with FM, 25 with RA, and 32 HC. Nine participants were excluded: 4 due to technical issues (1 FM, 3 RA), 4 due to co-morbidities that were not disclosed in the initial (phone) screening procedure (1 HC, 1 FM, 2 RA) and one due to Cannabis consumption (FM group). Thus, analyses included 81 participants: 30 FM, 20 RA and 31 HC. Subject's demographics are detailed in Table 4. There were no between groups differences in any of the demographic variables.

Table 4: Participants' demographic characteristics.

	HC (n=31)		FM (n=30)		RA (n=20)		Sig.
	M±SD	Median	M±SD	Median	M±SD	Median	
Age (years)	50.4±14.9	53.0	53.6±11.1	53.5	58±11.0	60.5	p=0.110
Body Mass Index (kg/m^2)	25.6±4.6	25.2	25.7±3.8	25.4	27.8±5.0	28.7	p=0.278
	fr	%	Fr	%	Fr	%	Sig.
MENSTRUAL							p=0.191
Follicular phase	9	29	6	20	2	10	
Luteal phase	2	6.5	7	23.3	1	5	
Undetermined	2	6.5	2	6.7	1	5	
Menoupase	18	58.1	15	50	16	80	
MARITAL STATUS							p=0.084
Single	11	35.5	3	10	1	5	
Married	11	35.5	19	63.3	9	45	
Unmarried	2	6.5	2	6.7	1	5	
separeted/divorced	6	19.4	5	16.7	7	35	
Widow	1	3.2	1	3.3	2	10	
COUPLE RELATION							p=0.554
Yes	16	51.6	19	63.3	10	50	
No	15	48.4	11	36.7	10	50	
EDUCATION							p=0.109
< 12years	18	58.1	22	73.3	17	85	
Graduation or master degree	13	41.9	8	26.7	3	15	
PROFESSIONAL STATUS							p=0.182
Active full-time worker	19	61.3	8	26.7	6	30	
Active part-time worker	2	6.5	1	3.3	1	5	
Homemaker	0	0	2	6.7	1	5	
Unemployed	4	12.9	4	13.3	2	10	
Retired	5	16.1	11	36.7	9	45	
Low	1	3.2	2	6.7			
other/missing			2	6.7	1	5	
FAMILY INCOME (euros/month)							p=0.084
< 500	6	19.4	5	16.7	5	25	
501-1500	22	7.1	14	46.7	10	50	
1501-2500	3	9.7	9	30.0	3	10	
>2500	0	0	2	6.7	4	15	

Fr: Frequency; sig: significance; HC: Healthy Control; FM: Fibromyalgia; RA: Rheumatoid Arthritis

Patients' medical and health related information is described in Table 5. Symptoms' duration did not significantly differ between FM and RA. As expected, pain (BPI) and quality of life (SF36) scores significantly differ between groups (Kruskal-Wallis Test). FM scores were significantly higher than HC scores ($p<0.001$) in all scales (Mann-Whitney). Significant differences were found between FM and RA in SF36 Mental Component and SF36 total score ($Z=-3.715$, $p<0.001$ and $Z=-3.068$, $p=0.002$, respectively). Lastly, significant differences were found between RA and HC in all questionnaires ($p<0.05$), except for the Mental subscale of the SF36 subscale ($Z=-1.666$, $p=0.96$). The results of disease-specific questionnaires (FIQ for FM and HAQ for RA) are presented as well (table 5).

Table 5: Patients' characteristics in each study group.

	HC (n=31)		**FM (n=30)**		**RA (n=20)**		**Sig.**
	M±SD	Median	M±SD	Median	M±SD	Median	
							FM-RA Wilcoxon comparisons
DISEASE DURATION (years)			18.7±11.9	16.5	17.9±12.0	17.0	p=0.883
CLINICAL PAIN	1.1±1.6	0.0	4.7±2.5	5.0	3.8±2.9	3.0	p=0.242
BPI							
Severity Scale	2.0±1.9	1.5	5.1±1.7	5.1	4.4±2.0	4.8	p=0.206
Interference Scale	1.4±2.1	0.4	5.5±2.3	5.6	3.8±2.9	3.1	**p=0.050**
SF-36							
SF-36 Total	77.0±13.5	78.2	36.7±17.6	33.1	56.9±20.6	59.2	**p=0.002**
SF-36 PCS	77.3±15.6	77.8	33.9±16.4	31.0	46.2±24.3	48.9	p=0.059
SF-36 MCS	76.6±14.8	76.8	39.6±22.3	38.1	67.5±20.4	69.5	**p<0.001**
FIQ							
Total Score			56.2±20.7	59.3			
Physical Functioning Scale			3.7±2.1	3.3			
Overall Impact Scale			6.0±2.9	5.7			
Symptoms Scale			3.0±3.3	2.9			
HAQ					0.95±0.7	1.0	
HADS							
HADS Total	8.9±4.7	8.0	18.9±8.0	17.0	13.5±7.1	13.0	**p=0.040**
HADS Anxiety	5.5±2.8	5.0	10.1±4.2	10.0	7.2±3.4	7.0	**p=0.034**
HADS Depression	3.4±2.3	3.0	8.8±4.8	7.0	6.3±5.1	5.0	p=0.053
MEDICATION							**Chi square FM-RA**
Pain	1	3.2	17	56.7	13	65	p=0.556
Psychotropics	4	12.9	26	86.7	5	25	**P<0.001**
Rheumatic	0	0	0	0	17	85	**P<0.001**
Hormonal	6	19.4	9	30	3	15	p=0.244

HC: Healthy Control; FM: Fibromyalgia; RA: Rheumatoid Arthritis; BPI: Brief Pain Inventory; SF-36: Short-Form Health Assessment; FIQ: Fibromyalgia Impact

Questionnaire; HAQ: Health Assessment Questionnaire; HADS: Hospital Depression and Anxiety Scale; Medication: Pain (Non-Steroids Anti-inflammatory, Analgesic, Weak Opioids); Psychotropics (Anticonvulsants, Antidepressives, Anxiolytics, Antipsychotics, Amphetamines); Rheumatic (AntiRheumatic, Biological, Corticosteroids), Hormonal (Thyroid-related, Oral contraceptives, Menoupause-related); Sig represents the results (p-value) of the Kruskal-Wallis Test.

6.4.2 Manipulation Check

Four participants were excluded because they did not believe they were playing Cyberball with real participants (2 from HC group, 2 from FM). Thus, all further analyses are based on data from 77 participants (29 HC, 28 FM and 20 RA).

6.4.3 Baseline Pain

Pain sensitivity at baseline, before Cyberball manipulation, is presented in Table 6. The intensity of stimulation needed to induce pain and unpleasantness rating of 1 (threshold) did not differ between the three study groups, nor the intensity of the stimuli needed to induce pain 5 (or unpleasantness 5).

Table 6: Baseline pain sensitivity.

	Entire Cohort (n=77)		HC (n=29)		FM (n=28)		RA (n=20)		Sig
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	
Pain Threshold (stimulus intensity)	75±63.00	60	75.52±53.29	60	79.63±86.80	50	68±33.02	70	p=0.709
Unpleasantness Theshold (stimulus intensity)	62.03±40.46	50	65.2±35.60	60	56.15±48.17	40	66.11±35.50	55	p=0.226
Pain 5 Stimulus Intensity	153.92±130.48	125	166.64±121.31	144	155.21±172.02	98	133.65±60.69	131	p=0.294
Pain 5 Perceived Pain	4.72±1.76	4.67	4.85±1.82	4.67	4.63±2.14	5	4.69±2.27	4.67	p=0.901
Pain 5 Perceived Unpleasantness	4.73±2.03	4.67	4.66±1.69	4.67	4.73±1.90	5	4.81±1.72	4.67	p=0.987

HC: Healthy Controls; FM: Fibromyalgia; RA: Rheumatoid Arthritis; Sig: results of between groups comparisons (Kruskal-Wallis Test).

6.4.4 Social Distress

Mean (±SD) and median social distress scores induced in response to the Inclusion and Exclusion conditions are depicted in Table 7. There were significant differences (Wilcoxon test) in social distress scores between Cyberball conditions (Z=-7.609, p<0.001). As expected, in the entire cohort, the Exclusion condition induced higher social distress than the Inclusion condition (Table 7). These differences in social distress scores between the Inclusion and the Exclusion condition of Cyberball remained significant when analyzed separately for each group (p<0.001). Moreover, the Kruskal-Wallis Test revealed no differences in social distress in the Exclusion condition between the 3 study groups, indicating that Inclusion and Exclusion induced similar effects in each group (Inclusion Condition: Chi Square=2.939, p=0.230; Exclusion Condition Chi Square= 5.435, p=0.066).

Table 7: Social distress scores.

	Entire Cohort (n=77)		HC (n=29)		FM (n=28)		RA (n=20)		Sig*
	M±SD	Median	M±SD	Median	M±SD	Median	M±SD	Median	
Social distress induced in Inclusion Condition	2.03±0.71	2	1.96±0.71	1.75	2.26±0.66	2.27	1.8±0.74	1.71	p=0.066
Social distress induced in Exclusion Condition	4.06±0.72	4	3.99±0.81	4	4.04±0.62	3.98	4.18±0.74	4.17	p=0.230
Sig**	**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**		

Sig*- results of between-groups comparisons (Kruskal-Wallis Test); Sig**-results of within-groups comparisons (Wilcoxon test).

6.4.5 The effects of social distress on pain

6.4.5.1 Between groups comparisons

Electrical pain

Changes in pain and unpleasantness in response to Cyberball manipulations are presented in Table 8. Significant differences between groups were found in the percentage of change in pain (Chi Square=7.979, p=0.019) and unpleasantness (Chi Square=7.752, p=0.021) after the Inclusion condition. Post-hoc analysis revealed that FM group differs in the percentage of change in pain (Z=-2.813, p=0.005) and unpleasantness (Z=-2.803, p=0.005) in Inclusion condition from the HC group. More specifically, pain and unpleasantness were reduced in the Inclusion condition in the HC and in RA groups but increased in the FM group. No other significant differences were found in either Exclusion or Inclusion conditions between groups.

Cold pain

No differences between groups were found in percentage of change in pain tolerance (Inclusion Z=0.196, p=0.907; Exclusion Z=1.108, p=0.575, Table 8), pain intensity (Inclusion Z=0.556, p=0.757; Exclusion Z=0.339, p=0.844) and unpleasantness intensity (Inclusion Z=3.023, p=0.221; Exclusion Z=0.397, p=0.820).

6.4.5.2 Within groups comparisons

Electrical pain

There were no significant differences in the percentage of change in pain (Z=-0.782, p=0.434) and unpleasantness (Z=-1.105, p=0.269) between the Inclusion and Exclusion condition in the entire cohort.

When each group was analyzed separately, significant differences in the percentage of change in both pain (Z=-2.2044, p=0.041) and unpleasantness (Z=-2.244, p=0.025) between Inclusion and Exclusion conditions were found in the FM group. Pain and unpleasantness were higher during the Inclusion condition while pain and

unpleasantness decreased during the Exclusion. There were no other within group differences.

Table 8: Percentage of change in pain and unpleasantness during each Cyberball condition.

	Change in Pain			Change in Unpleasantness		
	M±SD	Med	Sig.*	M±SD	Med	Sig.*
Entire Cohort (n=77)						
Inclusion	-4.31±37.17	1.09	**p=0.019**	-8.24±32.48	-3.97	p=**0.020**
Exclusion	-9.27±31.34	-8.33	p=0.985	-13.14±30.29	-12.17	p=0.895
Sig.**	0.434			p=0.269		
HC (n=29)						
Inclusion	-13.71±45.28	-12.78		-20.78±28.76	-16.67	
Exclusion	-13.66±33.31	-6.67		-18.04±30.89	-9.72	
Sig.**	p=0.545			p=0.411		
FM (n=28)						
Inclusion	7.50±26.04	15.00		2.86±31.98	11.11	
Exclusion	-9.04±23.56	-8.33		-14.34±21.13	-12.75	
Sig.**	**p=0.041**			**p=0.025**		
RA (n=20)						
Inclusion	-7.22±34.54	-7.06		-5.60±33.54	0.00	
Exclusion	-3.36±37.57	-13.23		-4.40±38.04	-13.23	
Sig.**	p=0.794			p=0.825		

HC: Healthy Control; FM: Fibromyalgia; RA: Rheumatoid Arthritis; Sig*: results of between groups comparisons (Kruskal-Wallis Test); Sig**: results of within groups comparisons (Wilcoxon test).

Cold pain

Within-subjects analysis in the entire cohort revealed no significant differences between study condition in the percentage of change in tolerance time (Z=0.921, p=0.357), pain (Z=0.813, p= 0.416) or unpleasantness (Z=-1.780, p=0.075). Within-subjects analysis separately in each group revealed that there were no significant differences between Inclusion and Exclusion in the change in time tolerance, pain and unpleasantness in each group.

6.4.6 Correlations between Social Distress and effects of Cyberball on pain

There were no significant correlations between Social Distress and change in pain measures, in electric or cold pain, in any group or condition.

6.5 Discussion

The current study aimed to assess the modulatory effects of social distress on pain in FM patients. Our hypothesis that FM patients will differently modulate pain in response to social distress manipulation was partially confirmed: In response to electrical stimulation, contrary to RA patients and HC, FM patients demonstrated increased pain and unpleasantness in the Inclusion condition.

To the best of our knowledge, this is the first study in which the effects of the Cyberball paradigm on pain sensitivity were assessed in chronic pain patients. Our main finding was that in FM, pain induced by electrical stimulation was increased by positive social events, suggesting altered pain modulation in response to positive events. Other studies use paradigms that manipulate emotional context by presenting positive, negative, neutral and pain-related pictures from the International Affective Picture System (Lang et al., 1999). Using this approach, Rhudy et al. (2013) demonstrated that while the negative and neutral pictures induce similar pain ratings between FM and RA patients, and HC, pain did not decrease in FM by the positive pictures, as occurred in the two other groups. Another study using the same picture paradigm similarly showed that

pain was not reduced in FM patients as in HC when viewing positive pictures (Kamping et al., 2013). These findings are in line with the current study results, suggesting that the deficits in pain modulation may be specific to modulation by positive social experiences.

The inability to modulate pain by positive emotions reported in Kamping et al. (2013) study was correlated with lower activation of the right secondary somatosensory, insula, orbitofrontal cortex and the ventral areas of anterior cingulated cortex. These brain areas are considered as part of the descending inhibitory system (Kamping et al., 2013). Most importantly, it was also found that the impairment in decreasing pain with positive pictures was correlated with a decrease in the activation of striatum. This is a brain area associated with reward (Drevets et al., 2001) and pain relief (Leknes et al., 2011) that has been related to impaired functioning in chronic pain conditions (Berger et al., 2014) and implicated in the transition from acute to chronic pain (Baliki et al., 2012; Mansour et al., 2013). More recently, an increase in activity of the ventral striatum was related to increased loneliness feelings and need for social connection (Inagaki et al., 2015).

Recent studies of pain anticipation and relief have found deficient activation of pain related areas, such as PAG, during anticipation of pain, as well as decreased activation of the ventral tegmental area in anticipation, stimulation and pain relief in FM patients (Loggia et al., 2014). These results are in line with Wood et al. (2007) describing that FM patients show abnormal dopamine release in this area in response to painful stimuli. Furthermore, it has been reported that the impact of cognitions (as catastrophizing) might be mediated by the recruitment of the lateral prefrontal cortex during the anticipation of pain (Loggia et al., 2015). Again, the reduced activation of this brain region suggests that FM patients have decreased ability to modulate pain in response to cognitive or emotional manipulations. However, other studies, using different paradigms, found efficient pain modulation in FM patients. For example, Montoya et al. (2004) reported a higher decrease in pain, comparing to migraines, when pain was induced in the presence of a significant other. Garza-Villarreal et al. (2014) found a decrease in pain unpleasantness ratings when patients hear pleasant music and Martinsen et al., (2014) showed that a Stroop distraction task induced similar pain

inhibition in FM and HC. Further studies thus need to investigate the reason for the divergent findings regarding emotional and cognitive pain modulation in FM.

Evidences of deficit in descending modulatory system in FM have been consistently reported using the more robust and standardized CPM paradigm (Kosec and Hansson, 1997; Lautenbacher and Rollman 1997; Julien et al., 2005; Staud et al., 2003). Impairment in CPM in other chronic pain conditions is not so clear. Similar efficiency in descending modulatory system in RA (Leffter et al., 2002), lower back pain (Julien et al., 2005) and migraine (De Tommaso et al., 2009) when compared to HC have been reported.

A finding of the current study deserve consideration: only electrical pain, but not cold pain, was affected by the manipulation. This might be related to differences in study design: While electrical pain was assessed both before and during each study condition, cold pain was assessed only during manipulation.

In conclusion, the current study found that in response to social inclusion, FM patients felt increased pain and unpleasantness, while HC and RA patients experienced decreased pain. This supports previous findings that FM patients have impaired descending pain modulation when exposed to positive emotions, and extend them by showing that this impairment can be triggered during social events. Future psychological interventions for FM patients might benefit from interventions directed to improve positive emotional and social processing.

Chapter 7

7. General Conclusion

The current dissertation aimed to contribute to the body of knowledge concerning the role of social dimensions in pain modulation in both healthy and chronic pain states. The studies reported in this dissertation were a tentative to relate two complex experiences, social distress and pain, and accordingly, two different fields of knowledge, social psychology and pain research.

The aim of the first study was to investigate the relationship between sensitivity to social distress and pain perception in healthy individuals. Our first hypothesis that individuals more sensitive to physical pain would be more sensitive to social distress was confirmed. In line with previous research (Eisenberger et al., 2006), it was found that sensitivity to social distress is correlated with sensitivity to the unpleasantness of physical pain, suggesting that there are some shared processes in the perception of these two experiences, most probably related to the shared emotional brain resources and mechanism from the medial pain system, that includes ACC and AI (Eisenberger, 2012).

The second hypothesis, that social distress manipulation would change pain perception was also confirmed. This study showed that Inclusion in a social game has a positive impact on pain experience, reducing the intensity of pain. The third hypothesis, that individual differences in attachment style would affect the relationship between social distress and pain was not confirmed. It was found that the relationship between the social distress manipulation and pain could not be explained by the individual differences theoretically considered related to sensitivity to pain, namely, attachment style or neuroticism.

Given that the relationship between emotional disorders, as depression and anxiety, have been clearly associated to the onset and development of chronic pain states

(Tracey et al., 2007; Wiech and Tracey, 2009; Goldenberg et al., 2010), the second study aimed to understand how social distress manipulation could modulate pain in chronic pain patients and if this manipulation could have a different impact depending on the chronic pain conditions considered.

Our main hypothesis that FM would demonstrate altered pain modulation under social manipulation was confirmed. Similarly to the first study, healthy individuals that were included in Cyberball demonstrated reduced pain. This was found in HC and RA patients, suggesting that engaging in the social game activated anti-nociceptive projections from the descending pain modulatory system. However, this was not found in the FM group, in which being included in the game did not reduce pain.

The differences reported between FM and the other groups are in line with previously described deficiencies in the recruitment of the descending modulatory system in this condition (Kosec and Hansson, 1997; Lautenbacher and Rollman, 1997; Julien et al., 2005) and with the described inability of reducing pain when viewing positive pictures, comparing to RA and HC (Rhudy et al., 2013; Kamping et al., 2013). Overall, this suggests the need to further detail the reasons why positive experiences cannot reduce pain in FM.

Recently, social connection needs have been related to striatum activations (Inagaki et al., 2015), a brain area that undergoes neuroplastic changes in the transitions from acute to chronic pain conditions (Baliki et al., 2012; Mansour et al., 2013), with concomitant behavioral changes in motivational behaviors (Berger et al., 2014) and that has been found to be impaired in FM patients (Wood et al., 2007). Another possible reason for a specific impair in positive emotions may be related to neurocognitive mechanism that may involve the insula cortex. Insula has been described has a key abnormal area in FM in most neuroimagem studies (Hsu et al., 2007; Harris et al., 2009; Napadow et al., 2010; Ichesco et al., 2014) and it may be possible that the recruitment of this brain area for processing negative emotional and interoceptive states may overcome the ability of recruiting this area for positive social emotions. Further studies are needed in order to assess the adequacy of this hypothesis.

The effect of social manipulations was restricted to one pain modality, most probably due to differences in the procedure, namely, not having an equal pain

assessment before and during the manipulations for cold pain modality. We believe that some of these inaccuracies in pain assessment may explain the divergent findings in previous studies that looked from relations between social variables and pain perception. For example, we found in this study that being excluded from Cyberball reduced pain perception, something that is the opposite of previous studies using this method (Eisenberger et al., 2006; Bernstein and Claypool, 2012). Nevertheless, new studies using different designs from acquisition of physiological variables suggest that inducing social distress may reduce interoception accuracy (Durlik and Tsakiris, 2015). Further studies with well validated paradigms relating social distress manipulations and pain simultaneously are a high challenge and should be improved in order to fully understand these relations. As such, additional evidences from studies in which social distress will be inflicted by other means, and pain assessment will be conducted by other modalities, could futher contribute to generalize our findings.

Based on the current studies we believe that social dimensions might represent a window for new intervention. There is evidence of the benefits of cognitive-behavioral therapy in FM, but usually these interventions focus on individual pain coping skills and do not include the improvement of social network skills. More research is needed in order to understand if and why these patients evidence problems with social inclusion, in order to develop adequate therapeutic approaches, eventually, confrontating barriers to positive social events, dysfunctional cognitions, as well as helping developing social networks and/or social skils.

In summary, the results presented in this dissertation demonstrated that social distress manipulation modulates pain experience in healthy individuals and in chronic pain patients. It has shown that the impact of this manipulation differ according to the pain condition and suggested that FM patients have impaired ability to recruit the descending pain modulatory system in the context of positive social events. These results emphasize the need for a greater focus on social situation of these patients. These evidences may support the development of new therapeutic approaches for FM that will take into consideration the effects of social distress. My hope is that my small contribution to this body of knowledge will support the efforts of the pain research

community to reduce suffering of Fibromyalgia patients, as well as of patients of other chronic pain conditions around the world.

REFERENCES

Ablin, K., & Clauw, D.J. (2009). From fibrositis to functional somatic syndromes to a bell-shaped curve of pain and sensory sensitivity: evolution of a clinical construct. *Rheum Dis Clin North Am, 35*, 233-251.

Ablin, J.N., Clauw, D.J., Lyden, A.K., Ambrose, K., Williams, D.A., Gracely, R.H., & Glass, J.M. (2013). Effects of sleep restriction and exercise deprivation on somatic symptoms and mood in healthy adults. *Clin Exp Rheumatol, 31*, S53-9.

Adler, G.K., Kinsley, B.T., Hurwitz, S., Mossey, C.J., & Goldenberg, D.L. (1999). Reduced hypothalamic-pituitary and sympathoadrenal responses to hypoglycemia in women with fibromyalgia syndrome. *Am J Med*, 106, 534-543.

Albe-Fessard, D., Berkley, K.J., Kruger, L., Ralston, H.J., 3rd, & Willis, W.D., Jr. (1985). Diencephalic mechanisms of pain sensation. *Brain Res, 356*, 217–296.

Allen, A.P., Kennedy, P.J., Cryan, J.F., Dinan, T.G., & Clarke, G. (2014). Biological and psychological markers of stress in humans: focus on the Trier Social Stress Test.*NeurosciBiobehav Rev., 38*, 94-124.

Andrews, M.H., & Matthews, S.G. (2004). Programming of the hypothalamo-pituitary-adrenal axis: serotonergic involvement. *Stress, 7*, 15-27.

Apkarian, A.V., Sosa, Y., Krauss, B.R., Thomas, P.S., Fredrickson, B.E., Levy, R.E., Harden, R.N., & Chialvo, D.R. (2004a). Chronic pain patients are impaired on an emotional decision-making task. *Pain, 108,*129-136.

Apkarian, A.V., Sosa, Y., Sonty, S., Levy, R.M., Harden, R.N., Parrish, T.B., & Gitelman, D.R. J. (2004b). Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *Neurosci., 24*, 10410-10415.

Apkarian, A.V., Bushnell, M.C., Treede, R.D., & Zubieta, J.K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *Eur. J. Pain, 9*, 463–484.

Apkarian, A.V., Hashmi, J.A., & Baliki, M.N. (2011). Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. *Pain, 152*, 49-64.

Apkarian, A.V., Baliki, M.N., & Farmer, M.A. (2013). Predicting transition to chronic pain.*Curr Opin Neurol., 26*, 360-367.

Arendt-Nielsen, L., Nie, H., Laursen, M.B., Laursen, B.S., Madeleine, P., Simonsen, O.H., & Graven-Nielsen, T. (2010). Sensitization in patients with painful knee osteoarthritis. *Pain, 149*, 573-581.

Arnold, L.M., Hudson, J.I., Keck, P.E., Auchenbach, M.B., Javaras, K.N., & Hess, E.V. (2006). Comorbidity of fibromyalgia and psychiatric disorders. *J Clin Psychiatry, 67*(8), 1219-1225.

Azevedo, L.F., Pereira, A.C., Dias, C., Agualusa, L., Lemos, L., Romão, J., Patto, T., Vaz-Serra, S., Abrunhosa, R., Carvalho, C.J, Cativo, M.C., Correia, D., Correia, J., Coucelo, G., Lopes, B.C., Loureiro, M.C., Silva, B., & Castro-Lopes, J.M. (2007). Tradução e adaptação cultural e estudo multicêntrico de validação de instrumentos para rastreio e validação do impacto da dor crónica. *Dor, 15,* 6-55.

Azevedo, L.F., Costa-Pereira, A., Mendonça, L., Dias, C.C., & Castro-Lopes, J.M. (2012). Epidemiology of chronic pain: a population-based nationwide study on its prevalence, characteristics and associated disability in Portugal. *J Pain, 13*(8), 773-783.

Azevedo, L.F., Costa-Pereira, A., Mendonça, L., Dias, C.C., & Castro-Lopes, J.M. (2014). The economic impact of chronic pain: a nationwide population-based cost-of-illness study in Portugal. *Eur J Health Econ*. 2014 Nov 22. [Epub ahead of print]

Baliki, M.N., Chialvo, D.R., Geha, P.Y., Levy, R.M., Harden, R.N., Parrish, T.B., & Apkarian, A.V. (2006). Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *J. Neurosci, 26*, 12165–12173.

Baliki, M.N., Geha, P.Y., Apkarian, A.V., & Chialvo, D.R. (2008). Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. J Neurosci, *28*(6), 1398-1403.

Baliki, M.N., Schnitzer, T.J., Bauer, W.R., & Apkarian, A.V. (2011). Brain morphological signatures for chronic pain*. PLoS One, 6*(10):e26010.

Baliki, M.N., Petre, B., Torbey, S., Herrmann, K.M., Huang, L., Schnitzer, T.J., Fields, H.L., & Apkarian, A.V. (2012). Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci*,*15*, 1117-1119.

Bannister, K., Bee, L.A., & Dickenson, A.H. (2009). Preclinical and early clinical investigations related to monoaminergic pain modulation. *Neurotherapeutics, 6*(4), 703-12.

Bantick, S.J., Wise, R.G., Ploghaus, A., Clare, S., Smith, S.M., & Tracey, I. (2002). Imaging how attention modulates pain in humans using functional MRI. *Brain, 125*, 310-319.

Baraniuk, J.N., Whalen, G., Cunningham, J., & Clauw, D.J. (2004). Cerebrospinal fluid levels of opioid peptides in fibromyalgia and chronic low back pain. *BMC Musculoskelet Disord, 9*, 5-48.

Bass, E.C., Stednitz, S.J., Simonson, K., Shen, T., & Gahtan, E. (2014). Physiological stress reactivity and empathy following social exclusion: a test of the defensive emotional analgesia hypothesis. *Soc Neurosci, 9*(5), 504-513.

Bazzichi, L., Dini, M., Rossi, A., Corbianco, S., De Feo, F., Giacomelli, C., Zirafa, C., Ferrari, C., Rossi, B., & Bombardieri, S. (2009). Muscle modifications in fibromyalgic patients revealed by surface electromyography (SEMG) analysis. *BMC Musculoskelet Disord, 15*, 10-36.

Becerra, L., Breiter, H.C., Wise, R., Gonzalez, R.G., & Borsook, D. (2001). Reward circuitry activation by noxious thermal stimuli. *Neuron, 32*(5), 927-946.

Becker, S., & Schweinhardt, P. (2012). Dysfunctional neurotransmitter systems in fibromyalgia, their role in central stress circuitry and pharmacological actions on these systems. *Pain Res Treat, 2012*, 741746.

Bederson, J.B., Fields, H.L., & Barbaro, N.M. (1990). Hyperalgesia during naloxone-precipitated withdrawal from morphine is associated with increased on-cell activity in the rostral ventromedial medulla. *Somatosens Mot Res, 7*(2), 185-203.

Bedson, J., & Croft, P.R. (2008). The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord. 2*, 9-116.

Benarroch, E.E. (2008). Descending monoaminergic pain modulation: bidirectional control and clinical relevance. *Neurology,* 71,217-21.

Bengtsson, A., Henriksson, K.G., & Larsson, J. (1986). Reduced high-energy phosphate levels in the painful muscles of patients with primary fibromyalgia. *Arthritis Rheum, 29*(7), 817-821.

Bengtsson, A., & Bengtsson, M. (1988). Regional sympathetic blockade in primary fibromyalgia. *Pain, 33*, 161-167.

Benka, J., Nagyova, I., Rosenberger, J., Macejova, Z., Lazurova, I., van der Klink, J.L., Groothoff, J.W., & van Dijk, J.P. (2015). Social participation in early and established rheumatoid arthritis patients. *Disabil Rehabil, 19*, 1-8.

Berger, S.E., Baria, A.T., Baliki, M.N., Mansour, A., Herrmann, K.M., Torbey, S., Huang, L., Parks, E.L., Schnizter, T.J., & Apkarian, A.V. (2014). Risky monetary behavior in chronic back pain is associated with altered modular connectivity of the nucleus accumbens. *BMC Res Notes*, 7,739.

Bernstein, M.J., & Claypool, H.M. (2012). Social exclusion and pain sensitivity: why exclusion sometimes hurts and sometimes numbs. *Pers Soc Psychol Bull., 38*, 185-196.

Bershad, A.K., Jaffe, J.H., Childs, E., & de Wit, H. (2015). Opioid partial agonist buprenorphine dampens responses to psychosocial stress in humans. *Psychoneuroendocrinology, 52*, 281-288.

Bessou, P., & Perl, E.R. (1969). Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *J Neurophysiol, 32*(6), 1025-1043.

Bingel, U., Lorenz, J., Schoell, E., Weiller, C., & Büchel, C. (2006). Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network, *Pain, 120*(1-2), 8-15.

Bingel, U., & Tracey, I. (2008). Imaging CNS modulation of pain in humans. *Physiology* (Bethesda), 23, 371-380.

Bingel, U., Wanigasekera, V., Wiech, K., Ni Mhuircheartaigh, R., Lee, M.C., Ploner, M., & Tracey, I. (2011). The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Sci Transl Med, 3*(70), 70ra14.

Bonenberger, M., Plener, P.L., Groschwitz, R.C., Grön, G., & Abler, B. (2015). Polymorphism in the μ-opioid receptor gene (OPRM1) modulates neural processing of physical pain, social rejection and error processing. *Exp Brain Res, 233*(9), 2517-2526.

Boothby, J.L., Thorn, B.E., Overduin, L.Y., & Ward, L.C. (2004). Catastrophizing and perceived partner responses to pain. *Pain, 109*(3), 500-506.

Borenstein, D. (2010). The role of the rheumatologist in managing pain therapy. *Nat Rev Rheumatol, 6*(4), 227-231.

Borsook, D., Upadhyay, J., Chudler, E.H., & Becerra, L. (2010) A key role of the basal ganglia in pain and analgesia--insights gained through human functional imaging. *Mol Pain, 13,* 6-27.

Bowlby J. (1973). *Attachment and loss* (Vol. 2). New York: Basic Books.

Bradley, L.A., & Alarcón, G.S. (1999). Is Chiari malformation associated with increased levels of substance P and clinical symptoms in persons with fibromyalgia? *Arthritis Rheum, 42*(12), 2731-2732.

Branco, J.C., Bannwarth, B., Failde, I., Abello Carbonell, J., Blotman, F., Spaeth, M., Saraiva, F., Nacci, F., Thomas, E., Caubère, J.P., Le Lay, K., Taieb, C., & Matucci-Cerinic, M. (2010). Prevalence of fibromyalgia: a survey in five European countries. *Semin Arthritis Rheum, 39*(6), 448-453.

Brennan, K.A., Clark, C.L., & Shaver, P.R. (1998). Self-report measurement of adult romantic attachment: An integrative overview. In: Simpson JA, Rholes WS, eds. Attachment theory and close relationships. New York: Guilford Press, 46–76.

Briand, L.A., Hilario, M., Dow, H.C., Brodkin, E.S., Blendy, J.A., & Berton, O. (2015). Mouse model of OPRM1 (A118G) polymorphism increases sociability and dominance and confers resilience to social defeat. *J Neurosci, 35*(8), 3582-3590.

Brown, C.A., El-Deredy, W., & Jones, A.K. (2014). When the brain expects pain: common neural responses to pain anticipation are related to clinical pain and distress in fibromyalgia and osteoarthritis. *Eur J Neurosci., 39*(4), 663-672.

Brown, J.L., Sheffield, D., Leary, M.R., & Robinson, M.E.(2003). Social support and experimental pain. *Psychosom Med, 65*(2), 276-283.

Buckelew, S.P., Parker, J.C., Keefe, F.J., Deuser, W.E., Crews, T.M., Conway, R., Kay, D.R., & Hewett, J.E. (1994). Self-efficacy and pain behavior among subjects with fibromyalgia. *Pain, 59*(3), 377-384.

Bungert, M., Koppe, G., Niedtfeld, I., Vollstädt-Klein, S., Schmahl, C., Lis, S., & Bohus, M. (2015). Pain Processing after Social Exclusion and Its Relation to Rejection Sensitivity in Borderline Personality Disorder. *PLoS One, 10*(8), e0133693.

Burckhardt, C.S., Clark, S.R., & Bennett, R.M. (1991). The Fibromyalgia Impact Questionnaire: Development and validation. *J Rheumatol*, 18,728-734.

Burgess, P.R., & Perl, E.R. (1967). Myelinated afferent fibres responding specifically to noxious stimulation of the skin. *J Physiol, 190*(3), 541-562.

Burgmer, M., Pogatzki-Zahn, E., Gaubitz, M., Wessoleck, E., Heuft, G., & Pfleiderer, B. (2009). Altered brain activity during pain processing in fibromyalgia. *Neuroimage, 44*(2), 502-508.

Burgmer, M., Pogatzki-Zahn, E., Gaubitz, M., Stüber, C., Wessoleck, E., Heuft, G., & Pfleiderer, B. (2010). Fibromyalgia unique temporal brain activation during experimental pain: a controlled fMRI Study. *J Neural Transm, 117(*1), 123-131.

Butler, R.K., & Finn, D.P. (2009). Stress-induced analgesia. *Prog Neurobiol, 88*(3), 184-202.

Cacioppo, S., Frum, C., Asp, E., Weiss, R.M., Lewis, J.W., & Cacioppo, J.T. (2013). A quantitative meta-analysis of functional imaging studies of social rejection. *Sci Rep, 3,* 20-27

Campbell, J., & Ehlert, U.(2012). Acute psychosocial stress: does the emotional stress response correspond with physiological responses? *Psychoneuroendocrinology, 37*(8), 1111-1134.

Canaipa, R., Treister, R., Lang, M., Moreira, J.M., & Catro Caldas, A. (2016). Feeling Hurt: Pain Sensitivity is Correlated with and Modulated by Social Distress. *Clin J Pain*, 32(1), 14-19.

Cano, A., Johansen, A.B., & Franz, A. (2005). Multilevel analysis of couple congruence on pain, interference, and disability. *Pain,118*(3), 369-379.

Carlino, E., Frisaldi, E., & Benedetti, F. (2014). Pain and the context. *Nat Rev Rheumatol, 10*(6), 348-355.

Caro, X.J., & Winter, E.F. (2014). Evidence of abnormal epidermal nerve fiber density in fibromyalgia: clinical and immunologic implications. Arthritis Rheumatol, 66(7), 1945-1954.

Cauda, F., Sacco, K., D'Agata, F., Duca, S., Cocito, D., Geminiani, G., Migliorati, F., & Isoardo, G. (2009a). Low-frequency BOLD fluctuations demonstrate altered thalamocortical connectivity in diabetic neuropathic pain. *BMC Neurosci, 10,* 138.

Cauda, F., Sacco, K., Duca, S., Cocito, D., D'Agata, F., Geminiani, G.C., & Canavero, S. (2009b). Altered resting state in diabetic neuropathic pain. *PLoS One, 4*(2), e4542.

Ceko, M., Gracely, J.L., Fitzcharles, M.A., Seminowicz, D.A., Schweinhardt, P., & Bushnell, M.C. (2015). Is a Responsive Default Mode Network Required for Successful Working Memory Task Performance? *J Neurosci, 35*(33), 11595-11605.

Chalaye, P., Lafrenaye, S., Goffaux, P., & Marchand, S. (2014). The role of cardiovascular activity in fibromyalgia and conditioned pain modulation. *Pain,155*,1064-1069.

Chiang, J.J., Eisenberger, N.I., Seeman, T.E., & Taylor, S.E. (2012). Negative and competitive social interactions are related to heightened proinflammatory cytokine activity. *Proc Natl Acad Sci USA*, 109(6), 1878-1882.

Choy, E.H. (2015). The role of sleep in pain and fibromyalgia. *Nat Rev Rheumatol, 11*(9), 513-520.

Christensen, B.N., & Perl, E.R. (1970). Spinal neurons specifically excited by noxious or thermal stimuli: marginal zone of the dorsal horn. *J Neurophysiol, 33(*2), 293-307.

Chudler, E.H., & Dong, W.K. (1995). The role of the basal ganglia in nociception and pain. *Pain, 60*(1), 3-38.

Cifre, I., Sitges, C., Fraiman, D., Muñoz, M.Á., Balenzuela, P., González-Roldán. A., Martínez-Jauand, M., Birbaumer, N., Chialvo, D.R., & Montoya, P. (2012). Disrupted functional connectivity of the pain network in fibromyalgia. *Psychosom Med, 74*(1), 55-62.

Clark, P., Burgos-Vargas, R., Medina-Palma, C., Lavielle, P., & Marina, F.F. (1998). Prevalence of fibromyalgia in children: a clinical study of Mexican children. *J Rheumatol, 25*(10), 2009-2014.

Clauw, D. (2015). Wilbert E. Fordyce Clinical Lecture: Fibromyalgia: A Disease, Common Pathway, or Rubbish? In *American Pain Society's 34th Scientific Meeting*, Palm Spring, LA.

Cleeland, C.S., & Ryan, K.M. (1994). Pain assessment: global use of the Brief Pain Inventory. *AnnAcadMedSingap23*,129–138.

Cook, D., Lange, G., Ciccone, D., Liu, W., Steffener, J., & Natelson, B. (2004). Functional imaging of pain in patients with primary fibromyalgia. *Journal of Rheumatology, 31*, 364-378.

Craig, A.D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci, 3*(8), 655-666.

Craig, A.D. (2003a). Pain mechanisms: labeled lines versus convergence in central processing. *Annu Rev Neurosci, 26*, 1-30.

Craig, A. D. (2003b). Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol, 13*(4), 500-505.

Craig, A.D. (2009). How do you feel--now? The anterior insula and human awareness. Nat *Rev Neurosci, 10*(1), 59-70.

Creamer, P., & Hochberg, M.C. (1997). Why does osteoarthritis of the knee hurt--sometimes? *Br J Rheumatol, 36*(7), 726-728.

Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., & Dolan, R.J. (2004). Neural systems supporting interoceptive awareness. *Nat. Neurosci. 7*, 189–195.

Dailey, P.A., Bishop, G.D., Russell, I.J., & Fletcher, E.M.(1990). Psychological stress and the fibrositis/fibromyalgia syndrome. *J Rheumatol, 17*(10), 1380-1385.

Dampney, R.A., Coleman, M.J., Fontes, M.A., Hirooka, Y., Horiuchi, J., Li, Y.W., Polson, J.W., Potts, P.D., & Tagawa, T. (2002). Central mechanisms underlying short- and long-term regulation of the cardiovascular system. *Clin Exp Pharmacol Physiol, 29*(4), 261-268.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., &Kelley, K.W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci, 9*(1), 46-56.

Dawes, J.M., & McMahon, S.B. (2013). Chemokines as peripheral pain mediators. *Neurosci Lett. 557*, 1-8.

De Felipe, C., Herrero, J.F., O'Brien, J.A., Palmer, J.A., Doyle, C.A., Smith, A.J., Laird, J.M., Belmonte, C., Cervero, F., & Hunt, S.P. (1998). Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. *Nature, 392*(6674), 394-397.

de Heer, E.W., Gerrits, M.M., Beekman, A.T., Dekker, J., van Marwijk, H.W., de Waal, M.W., Spinhoven, P., Penninx, B.W., & van der Feltz-Cornelis, C.M. (2014). The association of depression and anxiety with pain: a study from NESDA. *PLoS One, 9*(10), e106907.

Derbyshire, S.W., Whalley, G., Stenger, V.A., & Oakley, D.A. (2004). Cerebral activation during hypnotically induced and imagined pain. *Neuroimage, 23*(1), 392-401.

DeTommaso, M., Calabrese, R., Vecchio, E., De Vito Francesco, V., Lancioni, G., & Livrea, P. (2009). Effects of affective pictures on pain sensitivity and cortical responses induced by laser stimuli in healthy subjects and migraine patients. *Int J Psychophysio,74*, 139-48.

DeWall, C.N., & Baumeister, R.F. (2006). Alone but feeling no pain: Effects of social exclusion on physical pain tolerance and pain threshold, affective forecasting, and interpersonal empathy. *J Pers Soc Psychol, 91*, 1-15.

DeWall, C.N., Masten, C.L., Powell, C., Combs, D., Schurtz, D.R., & Eisenberger, N.I. (2012). Do neural responses to rejection depend on attachment style? An fMRI study. *Soc Cogn Affect Neurosci, 7*, 184-192.

Dickens, C., McGowan, L., & Dale, S. (2003). Impact of depression on experimental pain perception: a systematic review of the literature with meta-analysis. *Psychosom Med, 65*(3), 369-375.

Dickerson, S.S., & Kemeny, M.E. (2004). Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull, 130*(3), 355-391.

Dickey, R.P., & Minton, J.P. (1972). Levodopa relief of bone pain from breast cancer. *N Engl J Med, 286*(15), 843.

Djouhri, L., & Lawson, S.N. (2004). Abeta-fiber nociceptive primary afferent neurons: a review of incidence and properties in relation to other afferent A-fiber neurons in mammals. *Brain Res Brain Res Rev, 46*(2), 131-145.

Doppler, K., Rittner, H.L., Deckart, M., & Sommer, C. (2015). Reduced dermal nerve fiber diameter in skin biopsies of patients with fibromyalgia. *Pain*. [Epub ahead of print]

Drevets, W.C., Gautier, C., Price J.C., Kupfer, D.J., Kinahan, P.E., Grace, A.A., Price, J.L., & Mathis, C.A. (2001). Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry 49*,81-96.

Eccleston, C., & Crombez, G. (1999). Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol Bull, 125*(3), 356-366.

Eippert, F., Bingel, U., Schoell, E.D., Yacubian, J., Klinger, R., Lorenz, J., & Büchel, C. (2009). Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron, 63*(4), 533-543.

Eisenberger, N.I., Lieberman, M.D., & Williams, K.D. (2003). Does rejection hurt? An fMRI study of social exclusion. *Science, 302*, 290-292.

Eisenberger, N.I., & Lieberman, M.D. (2004). Why rejection hurts: a common neural alarm system for physical and social pain. *Trends Cogn Sci, 8*, 294-300.

Eisenberger, N.I., Jarcho, J.M., Lieberman, M.D., & Naliboff, B.D. (2006). An experimental study of shared sensitivity to physical pain and social rejection. *Pain 126*,132-138.

Eisenberger, N.I., Inagaki, T.K., Mashal, N.M., & Irwin, M.R. (2010). Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. *Brain Behav Immun, 24*(4), 558-563.

Eisenberger, N.I. (2012). The pain of social disconnection: Examining the shared neural underpinnings of physical and social pain. *Nat Rev Neurosci, 13*, 421-434.

Eisenberger, N.I. (2015). Social pain and the brain: controversies, questions, and where to go from here. *Annu Rev Psychol, 66*, 601-29.

Ertas, M., Sagduyu, A., Arac, N., Uludag, B., & Ertekin, C. (1998). Use of levodopa to relieve pain from painful symmetrical diabetic polyneuropathy. *Pain, 75*(2-3), 257-259.

Fayed, N., Garcia-Campayo, J., Magallón, R., Andrés-Bergareche, H., Luciano, J.V., Andres, E., & Beltrán, J. (2010). Localized 1H-NMR spectroscopy in patients with fibromyalgia: a controlled study of changes in cerebral glutamate/glutamine, inositol, choline, and N-acetylaspartate. *Arthritis Res Ther, 12*(4), R134.

Feraco, P., Bacci, A., Pedrabissi, F., Passamonti, L., Zampogna, G., Pedrabissi, F., Malavolta, N., & Leonardi, M. (2011). Metabolic abnormalities in pain-processing regions of patients with fibromyalgia: a 3T MR spectroscopy study. AJNR Am J Neuroradiol, 32(9), 1585-1590.

Fields, H.L., Vanegas, H., Hentall, I.D., & Zorman, G. (1983). Evidence that disinhibition of brain stem neurones contributes to morphine analgesia. *Nature, 306*(5944), 684-686.

Fields, H.L., & Basbaum, A.I. (2005). Central nervous system mechanisms of pain modulation. In R. Melzack, P. Wall (Eds.), *Textbook of Pain*, Churchill Livingstone, London, pp. 125–142.

Flor, H., Kerns, R.D., & Turk, D.C. (1987). The role of spouse reinforcement, perceived pain, and activity levels of chronic pain patients. *J Psychosom Res, 31*(2), 251-259.

Foerster, B.R., Petrou, M., Edden, R.A., Sundgren, P.C., Schmidt-Wilcke, T., Lowe, S.E., Harte, S.E., Clauw, D.J., & Harris, R.E. (2012). Reduced insular γ-aminobutyric acid in fibromyalgia. *Arthritis Rheum, 64*(2), 579-583.

Frank, R.G., Beck, N.C., Parker, J.C., Kashani, J.H., Elliott, T.R., Haut, A.E., Smith, E., Atwood, C., Brownlee-Duffeck, M., & Kay, D.R.(1988). Depression in rheumatoid arthritis. *J Rheumatol, 15*(6), 920-925.

Fries, J.F., Spitz, P., Kraines, R.G., & Holman, H.R. (1980). Measurement of patient outcome in arthritis*. Arthritis Rheum,23*,137–45.

Frisch, J.U., Häusser, J.A., & Mojzisch, A. (2015). The Trier Social Stress Test as a paradigm to study how people respond to threat in social interactions. *Front Psychol, 6*, 14.

Gabbott, P.L., Warner, T.A., Jays, P.R., Salway, P., & Busby, S.J. (2005). Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. *J Comp Neurol, 492*(2), 145-177.

Garza-Villarreal, E.A., Wilson, A.D., Vase, L., Brattico, E., Barrios, F.A., Jensen, T.S., Romero-Romo, J.I., & Vuust, P. (2014). Music reduces pain and increases functional mobility in fibromyalgia. *Front Psychol 5*,90.

Gauriau, C., & Bernard, J.F. (2004). A comparative reappraisal of projections from the superficial laminae of the dorsal horn in the rat: the forebrain. *J Comp Neurol, 468*(1), 24-56.

Gauriau, C., & Bernard, J.F. (2002). Pain pathways and parabrachial circuits in the rat. *Exp Physiol, 87*(2), 251-258.

Ge, H.Y., Nie, H., Graven-Nielsen, T., Danneskiold-Samsøe, B., &Arendt-Nielsen, L. (2012). Descending pain modulation and its interaction with peripheral sensitization following sustained isometric muscle contraction in fibromyalgia. *Eur J Pain16*, 196-203.

Gebhart, G.F. (2004). Descending modulation of pain. *Neurosci Biobehav Rev, 27*(8), 729-737.

Geha, P.Y., Baliki, M.N., Wang, X., Harden, R.N., Paice, J.A., &Apkarian, A.V. (2008). Brain dynamics for perception of tactile allodynia (touch-induced pain) in postherpetic neuralgia. *Pain, 138*(3), 641-656.

Geisser, M.E., Glass, J.M., Rajcevska, L.D., Clauw, D.J., Williams, D.A., Kileny, P.R.,&Gracely, R.H. (2008). A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls. *J Pain, 9*(5), 417-422.

Geniole, S.N., Carré, J.M., & McCormick, C.M. (2011). State, not trait, neuroendocrine function predicts costly reactive aggression in men after social exclusion and inclusion.*Biol Psychol, 87*(1), 137-145.

Gerdle, B., Larsson, B., Forsberg, F., Ghafouri, N., Karlsson, L., Stensson, N., & Ghafouri, B. (2014). Chronic widespread pain: increased glutamate and lactate concentrations in the trapezius muscle and plasma. *Clin J Pain, 30*(5), 409-20.

Giesecke, T., Gracely, R.H., Williams, D.A., Geisser, M.E., Petzke, F.W., &Clauw, D.J. (2005). The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis Rheum. 52*, 1577–1584.

Giovengo, S.L., Russell, I.J., & Larson, A.A. (1999). Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia.*J Rheumatol, 26*(7), 1564-1569.

Glass, J.M., Williams, D.A., Fernandez-Sanchez, M.L., Kairys, A., Barjola, P., Heitzeg, M.M., Clauw, D.J., & Schmidt-Wilcke, T. (2011). Executive function in chronic pain patients and healthy controls: different cortical activation during response inhibition in fibromyalgia. *J Pain. 12*(12), 1219-1229.

Godínez-Chaparro, B., Barragán-Iglesias, P., Castañeda-Corral, G., Rocha-González, H.I., & Granados-Soto, V. (2011). Role of peripheral 5-HT(4), 5-HT(6), and 5-HT(7) receptors in development and maintenance of secondary mechanical allodynia and hyperalgesia. *Pain, 152*(3), 687-97.

Goldberg, R., Pachas, W., & Keith, D. (1999). Relationship between traumatic events in childhood and chronic pain. *Disability and Rehabilitation, 21*, 23-30.

Goldenberg, D. L. (2010). The interface of pain and mood disturbances in the rheumatic diseases. *Semin Arthritis Rheum*, *40*, 15-31.

Gonzalez, B., Baptista, T.M., Branco, J.C., & Novo, R.F. (2015). Fibromyalgia characterization in a pychosocial approach. *Psychol Health Med, 20*(3), 363-368.

Good, M., Stanton-Hicks, M., Grass, J.A., Cranston Anderson, G., Choi, C., Schoolmeesters, L.J., &Salman, A. (1999). Relief of postoperative pain with jaw relaxation, music and their combination. *Pain, 81*(1-2), 163-72.

Gracely, R.H., Lota, L., Walter, D.J., & Dubner, R. (1988). A multiple random staircase method of psychophysical pain assessment. *Pain, 32*(1), 55-63.

Gracely, R.H., Petzke, F., Wolf, J.M., & Clauw, D.J. (2002). Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum, 46*(5), 1333-1343.

Gracely, R., Geisser, M., Giesecke, T., Grant, M., Petzke, F., Williams, D., & Clauw, D. (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain, 127*, 835-843.

Guedj, E., Taieb, D., Cammilleri, S., Lussato, D., de Laforte, C., Niboyet, J., & Mundler, O. (2007). 99mTc-ECD brain perfusion SPECT in hyperalgesic fibromyalgia. *Eur J Nucl Med Mol Imaging, 34*(1), 130-134.

Gündel, H., O'Connor, M.F., & Littrell, L. (2003). Functional neuroanatomy of grief: an FMRI study. *Am J Psychiatry, 160*, 1946-1953.

Gutz, L., Renneberg, B., Roepke, S., & Niedeggen, M. (2015). Neural processing of social participation in borderline personality disorder and social anxiety disorder.*J Abnorm Psychol, 124*(2), 421-31.

Gwilym, S.E., Keltner, J.R., Warnaby, C.E., Carr, A.J., Chizh, B., Chessell, I., & Tracey, I. (2009). Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis Rheum, 61*(9), 1226-1234.

Harris, R.E., Clauw, D.J., Scott, D.J., McLean, S.A., Gracely, R.H., & Zubieta, J.K. (2007). Decreased central mu-opioid receptor availability in fibromyalgia. *J Neurosci, 27*(37), 10000-10006.

Harris, R.E., Sundgren, P.C., Pang, Y., Hsu, M., Petrou, M., Kim, S.H., McLean, S.A., Gracely, R.H., & Clauw, D.J. (2008). Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. *Arthritis Rheum, 58*(3), 903-907.

Harris, R.E., Sundgren, P.C., Craig, A.D., Kirshenbaum, E., Sen, A., Napadow, V., & Clauw, D.J. (2009). Elevated insular glutamate in fibromyalgia is associated with experimental pain. *Arthritis Rheum, 60*(10), 3146-3152.

Hashmi, J.A., Baliki, M.N., Huang, L., Baria, A.T., Torbey, S., Hermann, K.M., Schnitzer, T.J., & Apkarian, A.V. (2013). Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain, 136*, 2751-2768.

Heinricher, M.M., Morgan, M.M., & Fields, H.L. (1992). Direct and indirect actions of morphine on medullary neurons that modulate nociception. *Neuroscience, 48*(3), 533-543.

Heinricher, M.M., Tavares, I., Leith, J.L., & Lumb, B.M. (2009). Descending control of nociception: Specificity, recruitment and plasticity. *Brain Res Rev, 60*(1), 214-225.

Howard, A.M., Landau, S., & Pryor, J.B. (2014). Peer bystanders to bullying: who wants to play with the victim? *J Abnorm Child Psychol, 42*(2), 265-276.

Hsu, D.T., Sanford, B.J., Meyers, K.K., Love, T.M., Hazlett, K.E., Wang, H., Ni, L., Walker, S.J., Mickey, B.J., Korycinski, S.T., Koeppe, R.A., Crocker, J.K., Langenecker, S.A., & Zubieta, J.K. (2013). Response of the μ-opioid system to social rejection and acceptance. *Mol Psychiatry, 18*(11), 1211-1217.

Hsu, M.C., Harris, R.E., Sundgren, P.C., Welsh, R.C., Fernandes, C.R., Clauw, D.J., & Williams. D.A. (2009). No consistent difference in gray matter volume between individuals with fibromyalgia and age-matched healthy subjects when controlling for affective disorder. *Pain, 143*(3), 262-267.

Hu, L., Xia, X.L., Peng, W.W., Su, W.X., F, Luo, Yuan, H., Chen, A.T., Liang, M., & Iannetti, G.D. (2015). Was It a Pain or a Sound? Across-species Variability in Sensory Sensitivity.*Pain* [Epub ahead of print]

Hudson, J.I., Goldenberg, D.L., Pope, H.G. Jr, Keck, P.E. Jr, & Schlesinger, L. (1992). Comorbidity of fibromyalgia with medical and psychiatric disorders. *Am J Med, 92*(4), 363-367.

Hughes, S., Jaremka, L.M., Alfano, C.M., Glaser, R., Povoski, S.P., Lipari, A.M., Agnese, D.M., Farrar, W.B., Yee, L.D., Carson, W.E. 3rd, Malarkey, W.B., & Kiecolt-Glaser, J.K. (2014). Social support predicts inflammation, pain, and depressive symptoms: longitudinal relationships among breast cancer survivors. *Psychoneuroendocrinology, 42*, 38-44.

Huskisson, E.C., & Hart, F.D. (1972). Pain threshold and arthritis. *Br Med J*, 4(5834), 193-195.

Iannetti, G.D., & Mouraux, A. (2010). From the neuromatrix to the pain matrix (and back). *Exp Brain Res, 205*(1), 1-12.

Iannetti, G.D., & Mouraux, A. (2011). Can the functional MRI responses to physical pain really tell us why social rejection "hurts"? *Proc Natl Acad Sci USA, 108*(30), E343.

IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp

Ichesco, E., Schmidt-Wilcke, T., Bhavsar, R., Clauw, D.J., Peltier, S.J., Kim, J., Napadow, V., Hampson, J.P., Kairys, A.E., Williams, D.A., & Harris, R.E. (2014). Altered resting state connectivity of the insular cortex in individuals with fibromyalgia. *J Pain, 15*(8), 815-826.

Iffland, B., Sansen, L.M., Catani, C., & Neuner, F. (2014). Rapid heartbeat, but dry palms: reactions of heart rate and skin conductance levels to social rejection. *Front Psychol, 5*, 956.

Ikeda, H., Mochizuki, K., & Murase, K. (2013). Astrocytes are involved in long-term facilitation of neuronal excitation in the anterior cingulate cortex of mice with inflammatory pain. *Pain, 154*(12), 2836-2843.

Imperato, A., Puglisi-Allegra, S., Casolini, P., & Angelucci, L. (1991). Changes in brain dopamine and acetylcholine release during and following stress are independent of the pituitary-adrenocortical axis. *Brain Res, 538*(1), 111-117.

Inagaki, T.K., Muscatell, K.A., Moieni, M., Dutcher, J.M., Jevtic, I., Irwin, M.R., & Eisenberger, N.I. (2015). Yearning for connection? Loneliness is associated with increased ventral striatum activity to close others. *SocCogn Affect Neurosci*. [Epub ahead of print]

Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. (2011). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington (DC): National Academies Press (US). Available from: http://www.ncbi.nlm.nih.gov/books/NBK92516/

Ivo, R., Nicklas, A., Dargel, J., Sobottke, R., Delank, K.S., Eysel, P., & Weber, B. (2013). Brain structural and psychometric alterations in chronic low back pain. *Eur Spine J, 22*(9), 1958-1964.

Jensen, K.B., Kosek, E., Petzke, F., Carville, S., Fransson, P., Marcus, H., Williams, S.C., Choy, E., Giesecke, T., Mainguy, Y., Gracely, R., & Ingvar, M. (2009). Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in rACC during provoked pain. *Pain, 144*(1-2), 95-100.

Jensen, K.B., Loitoile, R., Kosek, E., Petzke, F., Carville, S., Fransson, P., Marcus, H., Williams, S.C., Choy, E., Mainguy, Y., Vitton, O., Gracely, R.H., Gollub, R., Ingvar, M., & Kong, J. (2012). Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network. *Mol Pain, 8*, 32.

Jeon, H.A., & Friederici, A.D. (2015). Degree of automaticity and the prefrontal cortex. *Trends Cogn Sci, 19*(5), 244-250.

John, O.P., & Srivastava, S. (1999). The Big Five trait taxonomy: History, measurement, and theoretical perspectives. In Pervin, L.A., & John, O.P. (eds.) *Handbook of personality: Theory and research*. New York: Guilford, pp. 102-138.

Jones, A.K., & Derbyshire, S.W. (1997). Reduced cortical responses to noxious heat in patients with rheumatoid arthritis. *Ann Rheum Dis, 56*(10), 601-607.

Jones, A.K., Cunningham, V.J., Ha-Kawa, S., Fujiwara, T., Luthra, S.K., Silva, S., Derbyshire, S., & Jones, T. (1994). Changes in central opioid receptor binding in relation to inflammation and pain in patients with rheumatoid arthritis. *Br J Rheumatol, 33*(10), 909-916.

Jones, A.K., Huneke, N.T., Lloyd, D.M., Brown, C.A., & Watson, A. (2012). Role of functional brain imaging in understanding rheumatic pain. *Curr Rheumatol Rep, 14*(6), 557-567.

Jones, G.T., Atzeni, F., Beasley, M., Flüß, E., Sarzi-Puttini, P., & Macfarlane, G.J. (2015). The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. *Arthritis Rheumatol, 67*(2), 568-575.

Jørum, E. (1988). Analgesia or hyperalgesia following stress correlates with emotional behavior in rats. *Pain, 32*, 341-8.

Julien, N., Goffaux, P., Arsenault, P., & Marchandm S. (2005). Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain,* 114,295-302.

Kalisch, R., Wiech, K., Critchley, H.D., Seymour, B., O'Doherty, J.P., Oakley, D.A., Allen, P., & Dolan, R.J. (2005). Anxiety reduction through detachment: subjective, physiological, and neural effects. *J Cogn Neurosci, 17*(6), 874-83.

Kalyan-Raman, U.P., Kalyan-Raman, K., Yunus, M.B., & Masi, A.T. (1984). Muscle pathology in primary fibromyalgia syndrome: a light microscopic, histochemical and ultrastructural study. *J Rheumatol, 11*(6), 808-813.

Kamping, S., Bomba, I.C., Kanske, P., Diesch, E., & Flor, H. (2013).Deficient modulation of pain by a positive emotional context in fibromyalgia patients. *Pain*,*154*, 1846-1855.

Kantamneni, S. (2015). Cross-talk and regulation between glutamate and GABAB receptors.*Front Cell Neurosci, 9*, 135.

Karremans, J.C., Heslenfeld, D.J., van Dillen, L.F., & Van Lange, P.A. (2011). Secure attachment partners attenuate neural responses to social exclusion: an fMRI investigation. *Int J Psychophysiol, 81*, 44-50.

Kawasaki, Y., Kohno, T., Zhuang, Z.Y., Brenner, G.J., Wang, H., Van Der Meer, C., Befort, K., Woolf, C.J., & Ji, R.R. (2004). Ionotropic and metabotropic receptors, protein kinase A, protein kinase C, and Src contribute to C-fiber-induced ERK activation and cAMP response element-binding protein phosphorylation in dorsal horn neurons, leading to central sensitization. *J Neurosci, 24*(38), 8310-8321.

Kelly, M., McDonald, S., & Rushby, J. (2012). All alone with sweaty palms--physiological arousal and ostracism. *Int J Psychophysiol, 83*, 309-314.

Kemeny, M.E. (2009). Psychobiological responses to social threat: evolution of a psychological model in psychoneuroimmunology. *Brain BehavImmun, 23*, 1-9.

Kendler, K.S., Hettema, J.M., Butera, F., Gardner, C.O., & Prescott, C.A. (2003). Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. *Arch Gen Psychiatry, 60*(8), 789-796.

Kerns, R.D., Haythornthwaite, J., Southwick, S., & Giller, E.L.Jr. (1990). The role of marital interaction in chronic pain and depressive symptom severity. *J Psychosom Res, 34*(4), 401-408.

Kersting, A., Ohrmann, P., Pedersen, A., Kroker, K., Samberg, D., Bauer, J., Kugel, H., Koelkebeck, K., Steinhard, J., Heindel, W., Arolt, V., & Suslow, T.(2009) Neural activation underlying acute grief in women after the loss of an unborn child. *Am J Psychiatry, 166*, 1402-10.

Kirschbaum, C., Pirke, K.M., & Hellhammer, D.H. (1993). The 'Trier Social Stress Test'--a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology, 28*, 76-81.

Kong, J., Spaeth, R.B., Wey, H.Y., Cheetham, A., Cook, A.H., Jensen, K., Tan, Y., Liu, H., Wang, D., Loggia, M.L., Napadow, V., Smoller, J.W., Wasan, A.D., & Gollub, R.L. (2013). S1 is associated with chronic low back pain: a functional and structural MRI study. *Mol Pain, 21*, 9-43.

Konttinen, Y.T., Honkanen, V.E., Grönblad, M., Keinonen, M., Santavirta, N., & Santavirta, S. (1992). The relation of extraarticular tenderness to inflammatory joint disease and personality in patients with rheumatoid arthritis. *J Rheumatol, 19*(6), 851-855.

Kool, M.B., & Geenen, R. (2012). Loneliness in patients with rheumatic diseases: the significance of invalidation and lack of social support. *J Psychol, 146*, 229-241.

Kosek, E., Ekholm, J., & Hansson, P. (1995). Increased pressure pain sensibility in fibromyalgia patients is located deep to the skin but not restricted to muscle tissue. P*ain, 63*(3), 335-339.

Kosek, E., & Hansson, P. (1997). Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. *Pain, 70*, 41-51.

Kosek, E., & Ordeberg, G. (2000). Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. *Pain, 88*(1), 69-78.

Kosmidis, M.L., Koutsogeorgopoulou, L., Alexopoulos, H., Mamali, I., Vlachoyiannopoulos, P.G., Voulgarelis, M., Moutsopoulos, H.M., Tzioufas, A.G., & Dalakas, M.C. (2014). Reduction of Intraepidermal Nerve Fiber Density (IENFD) in the skin biopsies of patients with fibromyalgia: a controlled study. *J Neurol Sci, 347(1-2*), 143-147.

Kregel, J., Meeus, M., Malfliet, A., Dolphens, M., Danneels, L., Nijs, J., & Cagnie, B. (2015). Structural and functional brain abnormalities in chronic low back pain: A systematic review. *Semin Arthritis Rheum, 45*(2), 229-237.

Kross, E., Egner, T., Ochsner, K., Hirsch, J., & Downey, G. (2007). Neural dynamics of rejection sensitivity. *J. Cogn. Neurosci, 19*, 945–956.

Kross, E., Berman, M.G., Mischel, W., Smith, E.E., & Wager, T.D. (2011). Social rejection shares somatosensory representations with physical pain. *Proc. Natl Acad. Sci. USA, 108,*6270–6275.

Kuchinad, A., Schweinhardt, P., Seminowicz, D.A., Wood, P.B., Chizh, B.A., & Bushnell, M.C. (2007). Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? *J Neurosci, 27(*15), 4004-4007.

Kulkarni, B., Bentley, D.E., Elliott, R., Julyan, P.J., Boger, E., Watson, A., Boyle, Y., El-Deredy, W., & Jones, A.K. (2007). Arthritic pain is processed in brain areas concerned with emotions and fear. *Arthritis Rheum, 56*(4), 1345-1354.

Kwiatek, R., Barnden, L., Tedman, R., Jarrett, R., Chew, J., Rowe, C., & Pile, K. (2000). Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. *Arthritis Rheum, 43*(12), 2823-2833.

Landa, A., Peterson, B.S., & Fallon, B.A. (2012). Somatoform pain: a developmental theory and translational research review. *Psychosom Med, 74*(7), 717-727.

Lang, P.J., Bradley, M.M., & Cuthbert, B.N. (1990). Emotion, attention, and the startle reflex. *Psychol Rev, 97(*3), 377-395.

Lang, P.J. (1995). The emotion probe. Studies of motivation and attention. *Am Psychol, 50*(5), 372-385.

Lang, P.J., Bradley, M.M., & Cuthbert, B.N. (1999). *International affective picture system (IAPS): Technical manual and affective ratings*. University of Florida, Center for Research in Psychophysiology (Gainesville).

Laske, C., Stransky, E., Eschweiler, G., Klein, R., Wittorf, A., Leyhe, T., Richartz, E., Kohler, N., Bartels, M., Buchkremer, G., & Schott, K. (2007). Increased BDNF serum concentration in fibromyalgia with or without depression or antidepressants. *Journal of Psychiatr Res, 41(7)*, 600-605.

Lautenbacher, S., Rollman, G.B., & McCain, G.A. (1994). Multi-method assessment of experimental and clinical pain in patients with fibromyalgia. *Pain, 59*(1), 45-53.

Lautenbacher, S., & Rollman, G.B. (1997). Possible deficiencies of pain modulation in fibromyalgia. *Clin J Pain, 13*, 189-96.

Lee, K.H., Blaha, C.D., Harris, B.T., Cooper, S., Hitti, F.L., Leiter, J.C., Roberts, D.W., & Kim, U. (2006). Dopamine efflux in the rat striatum evoked by electrical stimulation of the subthalamic nucleus: potential mechanism of action in Parkinson's disease. *Eur J Neurosci, 23*(4), 1005-1014.

Lee, Y.C., Nassikas, N.J., & Clauw, D.J. (2011). The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arthritis Res Ther, 13*(2), 211.

Lee, Y.C., Frits, M.L., Iannaccone, C.K., Weinblatt, M.E., Shadick, N.A., Williams, D.A., & Cui, J. (2014). Subgrouping of patients with rheumatoid arthritis based on pain, fatigue, inflammation, and psychosocial factors. *Arthritis Rheumatol, 66*(8), 2006-2014.

Leffler, A.S., Kosek, E., Lerndalm T., Nordmarkm B., & Hanssonm P. (2002). Somatosensory perception and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from rheumatoid arthritis. *Eur J Pain, 6*,161-76.

Leknes, S., Lee, M., Berna, C., Andersson, J., & Tracey, I. (2011). Relief as a reward: hedonic and neural responses to safety from pain. *PLoS One, 6*, e17870.

Lerma, C., Martinez, A., Ruiz, N., Vargas, A., Infante, O., & Martinez-Lavin, M. (2011). Nocturnal heart rate variability parameters as potential fibromyalgia biomarker: correlation with symptoms severity. *Arthritis Res Ther, 13(*6), R185.

Lima, D., & Almeida, A. (2002). The medullary dorsal reticular nucleus as a pronociceptive centre of the pain control system. *Prog Neurobiol, 66*(2), 81-108

Loggia, M.L., Kim, J., Gollub, R.L., Vangel, M.G., Kirsch, I., Kong, J., Wasan, A.D., & Napadow, V. (2013). Default mode network connectivity encodes clinical pain: an arterial spin labeling study. *Pain, 154*(1), 24-33.

Loggia, M.L., Berna, C., Kim, J., Cahalan, C.M., Gollub, R.L., Wasan, A.D., Harris, R.E., Edwards, R.R., & Napadow., V. (2014). Disrupted brain circuitry for pain-related reward/punishment in fibromyalgia.*Arthritis Rheumatol,* 66, 203-12.

Loggia, M.L., Berna, C., Kim, J., Cahalan, C.M., Martel, M.O., Gollub, R.L., Wasan, A.D., Napadow, V., & Edwards, R.R. (2015). The Lateral Prefrontal Cortex Mediates the Hyperalgesic Effects of Negative Cognitions in Chronic Pain Patients. *J Pain, 16*(8), 692-699.

López-Martínez, A.E., Esteve-Zarazaga, R., & Ramírez-Maestre, C. (2008). Perceived social support and coping responses are independent variables explaining pain adjustment among chronic pain patients. *J Pain, 9*(4), 373-379.

Lorenz J., Cross D., Minoshima S, Morrow T, Paulson P, & Casey K.L. (2002). A unique representation of heat allodynia in the human brain. *Neuron, 35*,383–93.

Lorenz, J., Minoshima, S., & Casey, K.L. (2003). Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain, 126*(Pt 5), 1079-91.

Luerding, R., Weigand, T., Bogdahn, U., & Schmidt-Wilcke, T. (2008). Working memory performance is correlated with local brain morphology in the medial frontal and anterior cingulate cortex in fibromyalgia patients: structural correlates of pain-cognition interaction. *Brain, 131*(Pt 12), 3222-31.

Lutz, J., Jäger, L., de Quervain, D., Krauseneck, T., Padberg, F., Wichnalek, M., Beyer, A., Stahl, R., Zirngibl, B., Morhard, D., Reiser, M., & Schelling, G. (2008). White and gray matter abnormalities in the brain of patients with fibromyalgia: a diffusion-tensor and volumetric imaging study. *Arthritis Rheum, 58*(12), 3960-3969.

Macdonald, G., & Leary, M. R. (2005). Why does social exclusion hurt? The relationship between social and physical pain. *Psychol Bull, 131*, 202-23.

MacDonald, G. (2008). Use of pain threshold reports to satisfy social needs. *Pain Res Manag, 13*, 309-19.

Malinen, S., Vartiainen, N., Hlushchuk, Y., Koskinen, M.,Ramkumar, P., Forss, N., Kalso, E., & Hari, R. (2010). Aberrant temporal and spatial brain activity during rest in patients with chronic pain. *Proc Natl Acad Sci USA, 107*(14), 6493-6497.

Mansour, A.R., Baliki, M.N., Huang, L., Torbey, S., Herrmann, K.M., Schnitzer, T.J., & Apkarian, A.V. (2013). Brain white matter structural properties predict transition to chronic pain. *Pain, 154*, 2160-2168.

Marchese, G., Pittau, B., Casu, G., Peddio, G., Spada, G.P., Pira, M., Deriu, A., Portesani, F., Pisu, C., Lazzari, P., & Pani, L. (2010). A comparison of continuous subcutaneous paliperidone infusion and repeated subcutaneous injection of risperidone free-base in rats. *Eur Psychiatry, 25*(2), 92-100.

Marouf, R., Caron, S., Lussier, M., Bherer, L., Piché, M., & Rainville, P. (2014) Reduced pain inhibition is associated with reduced cognitive inhibition in healthy aging. *Pain, 155*(3), 494-502.

Martikainen, I.K., Nuechterlein, E.B., Peciña, M., Love, T.M., Cummiford, C.M., Green, C.R., Stohler, C.S., & Zubieta, J.K. (2015). Chronic Back Pain Is Associated with Alterations in Dopamine Neurotransmission in the Ventral Striatum. *J Neurosci, 35*(27), 9957-9965.

Martinez-Lavin, M., & Hermosillo, A. (2000). Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. *Semin Arthritis Rheum, 29*, 197-199.

Martínez-Martínez, L.A., Mora, T., Vargas, A., Fuentes-Iniestra, M., & Martínez-Lavín, M. (2014). Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. *J Clin Rheumatol, 20*(3), 146-150.

Martinsen, S., Flodin, P., Berrebi, J., Löfgren, M., Bileviciute-Ljungar, I., Ingvar, M., Fransson, P., & Kosek, E. (2014). Fibromyalgia patients had normal distraction related pain inhibition but cognitive impairment reflected in caudate nucleus and hippocampus during the Stroop Color Word Test. *PLoSOne, 9*, e108637.

Mas, A.J., Carmona, L., Valverde, M., Ribas, B., & EPISER Study Group. (2008). Prevalence and impact of fibromyalgia on function and quality of life in individuals from the general population: results from a nationwide study in Spain. *Clin Exp Rheumatol, 26*(4), 519-526.

Mattson, M.P., Guthrie, P.B., & Kater, S.B. (1989). A role for Na^{+}-dependent Ca^{2+} extrusion in protection against neuronal excitotoxicity. *FASEB J, 3*(13), 2519-26.

McBeth, J., Macfarlane, G., Benjamim, S., Morris, S., & Silman, A. (1999). The association between tender points, psychologycal distress, and adverse childhood experiences: a community-based study. *Arthritis and Rheumatism, 42*, 1397-1404.

McBeth, J., Chiu, Y., Silman, A., Ray, D., Morris, R., Dickens, C., Gupta, A., & Macfarlane, G. (2005). Hypothalamic-pituitary-adrenal stress axis function and the relationship with chronic widespread pain and its antecedents. *Arthritis Res and Ther, 7*(5), 992-1000.

McCaul, K.D., & Haugtvedt, C. (1982). Attention, distraction, and cold-pressor pain. *J Pers Soc Psychol, 43*(1), 154-62.

McIntyre, T., Pereira, M.G., Soares, V., Gouveia, J., & Silva, S. (1999). *Escala de ansiedade e depressão hospitalar. Versão portuguesa de investigação.* Universidade do Minho: Departamento de Psicologia.

McLean, S., Williams, D., Stein, P., Harris, R., Lyden, A., Whalen, G., Park, K., Liberzon, I., Sen, A., Gracely, H., Baraniuk, J., & Clauw, D. (2006). Cerebrospinal fluid cortocotropin-releasing factor concentration is associated with pain but not fatigue symptoms in patients with fibromyalgia. *Neuropsychopharmacology, 31*, 2776-2782.

McQuaid, R.J., McInnis, O.A., Matheson, K., & Anisman, H. (2015). Distress of ostracism: oxytocin receptor gene polymorphism confers sensitivity to social exclusion. *Soc Cogn Affect Neurosci, 10*(8), 1153-1159.

Meagher, M.W., Arnau, R.C., & Rhudy, J.L. (2001). Pain and emotion: effects of affective picture modulation. *Psychosom Med, 63*(1), 79-90.

Meeus, M., Hermans, L., Ickmans, K., Struyf, F., Van Cauwenbergh, D., Bronckaerts, L., De Clerck, L.S., Moorken, G., Hans, G., Grosemans, S., & Nijs, J. (2015). Endogenous pain modulation in response to exercise in patients with rheumatoid arthritis, patients with chronic fatigue syndrome and comorbid fibromyalgia, and healthy controls: a double-blind randomized controlled trial. *Pain Pract, 15*(2), 98-106.

Melzack, R., & Wall, P.D. (1965). Pain mechanisms: a new theory. *Science, 150*(3699), 971-979.

Melzack, R., & Torgerson, W.S. (1971). On the language of pain. *Anesthesiology, 34*, 50–59.

Merskey, H. (1994). Logic, truth and language in concepts of pain. *Qual Life Res, 3*, S69-76.

Mikulincer, M., & Florian, V. (1998). The relationship between adult attachment styles and emotional and cognitive reactions to stressful events. In Simpson J, Rholes S, (eds.)*Attachment theory and close relationships.* New York: Guilford Press, pp. 143–165.

Millan, M.J. (1999). The induction of pain: an integrative review. *Prog Neurobiol, 57*(1), 1-164.

Millan, M.J. (2002). Descending control of pain. *Prog Neurobiol, 66*(6), 355-474.

Miron, D., Duncan, G.H., & Bushnell, M.C.(1989). Effects of attention on the intensity and unpleasantness of thermal pain. *Pain, 39*(3), 345-52.

Moieni, M., Irwin, M.R., Jevtic, I., Breen, E.C., & Eisenberger, N.I. (2015a). Inflammation impairs social cognitive processing: A randomized controlled trial of endotoxin. *Brain Behav Immun, 48*, 132-138.

Moieni, M., Irwin, M.R., Jevtic, I., Olmstead, R., Breen, E.C., & Eisenberger, N.I. (2015b). Sex differences in depressive and socioemotional responses to an inflammatory challenge: implications for sex differences in depression. *Neuropsychopharmacology, 40*(7), 1709-16.

Moldofsky, H., Scarisbrick, P., England, R., & Smythe, H. (1975). Musculoskeletal symptoms and non REM sleep disturbance in patients with “fibrositis syndrome” and healthy subjects. *Psychosomatic Medicine, 34*, 341-351.

Moldofsky, H., & Scarisbrick, P. (1976). Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. *Psychosom Med, 38*(1), 35-44.

Moldofsky, H. (2008). The significance, assessment, and management of nonrestorative sleep in fibromyalgia syndrome. *CNS Spectr, 13*(3), 22-26

Monroe, S.M., Rohde, P., Seeley, J.R. & Lewinsohn, P.M. (1999). Life events and depression in adolescence: relationship loss as a prospective risk factor for first onset of major depressive disorder. *J Abnorm Psychol, 108*, 606–614.

Montoya, P., Larbig, W., Braun, C., Preissl, H., & Birbaumer, N. (2004). Influence of social support and emotional context on pain processing and magnetic brain responses in fibromyalgia. *ArthritisRheum 50*, 4035-4044.

Moreira, J.M. (2002). *Altera pars auditur: The dual influence of the quality of relationships upon positive and negative aspects of coping with stress*. Unpublished doctoral dissertation, Universidade de Lisboa, Portugal.

Moreira, J.M., Lind, W., Santos, M.J., Moreira, A.R., Gomes, M.J., Justo, J., Oliveira, A.P., Filipe, L.A., & Faustino, M. (2006). "Experiências em Relações Próximas", um questionário de avaliação das dimensões básicas dos estilos de vinculação nos adultos: Tradução e validação para a população Portuguesa. *Laboratório de Psicologia, 4*, 3-27.

Mountz, J.M., Bradley, L.A., Modell, J.G., Alexander, R.W., Triana-Alexander, M., Aaron, L.A., Stewart, K.E., Alarcón, G.S., & Mountz, J.D. (1995). Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. *Arthritis Rheum, 38*(7), 926-38.

Mutso, A.A., Petre, B., Huang, L., Baliki, M.N., Torbey, S., Herrmann, K.M., Schnitzer, T.J., & Apkarian, A.V. (2014). Reorganization of hippocampal functional connectivity with transition to chronic back pain. *J Neurophysiol, 111*(5), 1065-1076.

Nagy, A., Eördegh, G., Paróczy, Z., Márkus, Z., & Benedek, G. (2006). Multisensory integration in the basal ganglia. *Eur J Neurosci, 24*(3), 917-924.

Napadow, V., LaCount, L., Park, K., As-Sanie, S., Clauw, D.J., & Harris, R.E.(2010). Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis Rheum, 62*(8), 2545-2555.

Navratilova,E., &Porreca, F. (2014). Reward and motivation in pain and pain relief. *Nat Neurosci, 17*(10), 1304-1312.

O'Driscoll, S.L., & Jayson, M.I. (1974). Pain threshold analysis in patients with osteoarthrosis of hip. *Br Med J., 3*(5933), 714-715.

Oaklander, A.L., Herzog, Z.D., Downs, H.M., & Klein, M.M. (2013). Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain, 154*(11), 2310-2316.

O'Connor, M.F., Wellisch, D.K., Stanton, A.L., Eisenberger, N.I., Irwin, M.R., & Lieberman, M.D. (2008). Craving love? Enduring grief activates brain's reward center. *Neuroimage, 42*(2), 969-972.

Okifuji, A., Turk, D.C., & Sherman, J.J. (2000). Evaluation of the relationship between depression and fibromyalgia syndrome: why aren't all patients depressed? *J Rheumatol, 27*(1), 212-229.

Onoda, K., Okamoto, Y., Nakashima, K., Nittono, H., Yoshimura, S., Yamawaki, S., Yamaguchi, S., & Ura, M. (2010). Does low self-esteem enhance social pain? The relationship between trait self-esteem and anterior cingulate cortex activation induced by ostracism. *Soc Cogn Affect Neurosci, 5*(4), 385-391.

Oosterman, J.M., Dijkerman, H.C., Kessels, R.P., & Scherder, E.J. (2010). A unique association between cognitive inhibition and pain sensitivity in healthy participants. *Eur J Pain, 14*(10), 1046-1050.

Opris, I., & Casanova, M.F. (2014). Prefrontal cortical minicolumn: from executive control to disrupted cognitive processing. *Brain, 137*(Pt 7), 1863-75.

Pais-Ribeiro, J. (2005). *O importante é a saúde: estudo de adaptação de um instrumento para avaliar a percepção de saúde*. Lisboa: Fundação Merck.

Palazzo, E., Marabese, I., Soukupova, M., Luongo, L., Boccella, S., Giordano, C., de Novellis, V., Rossi, F., & Maione, S. (2011). Metabotropic glutamate receptor subtype 8 in the amygdala modulates thermal threshold, neurotransmitter release, and rostral ventromedial medulla cell activity in inflammatory pain. *J Neurosci, 31*(12), 4687-4697.

Panksepp, J., Herman, B., Conner, R., Bishop, P., & Scott, J.P. (1978). The biology of social attachments: opiates alleviate separation distress, *Biol Psychiatry, 13*(5), 607-618.

Panksepp, J. (1998). *Affective Neuroscience: The Foundations of Human and Animal Emotions*. Oxford: University Press, 1998.

Park, C., Kim, J.H., Yoon, B.E., Choi, E.J., Lee, C.J., & Shin, H.S. (2010). T-type channels control the opioidergic descending analgesia at the low threshold-spiking GABAergic neurons in the periaqueductal gray. *Proc Natl Acad Sci USA, 107*(33), 14857-14862.

Parks, E.L., Geha, P.Y., Baliki, M.N., Katz, J., Schnitzer, T.J., & Apkarian, A.V. (2011). Brain activity for chronic knee osteoarthritis: dissociating evoked pain from spontaneous pain. *Eur J Pain, 15*(8): 843.e1-14.

Paul-Savoie, E., Marchand, S., Morin, M., Bourgault, P., Brissette, N., Rattanavong, V., Cloutier, C., Bissonnette, A., & Potvin, S. (2012). Is the deficit in pain inhibition in fibromyalgia influenced by sleep impairments? *Open Rheumatol J*. 6,296-302.

Paulus, M.P., & Stein, M.B. (2006). An insular view of anxiety. *Biol Psychiatry, 60*(4), 383-387.

Penhoat, M., Saraux, A., Le Goff, B., Augereau, P., Maugars, Y., & Berthelot, J.M. (2014). High pain catastrophizing scores in one-fourth of patients on biotherapy for spondylarthritis or rheumatoid arthritis. *Joint Bone Spine, 81*(3), 235-239.

Pertovaara, A. (2013). The noradrenergic pain regulation system: a potential target for pain therapy. *Eur J Pharmacol, 716*(1-3), 2-7.

Petrou, M., Harris, R.E., Foerster, B.R., McLean, S.A., Sen, A., Clauw, D.J., & Sundgren, P.C. (2008). Proton MR spectroscopy in the evaluation of cerebral metabolism in patients with fibromyalgia: comparison with healthy controls and correlation with symptom severity. *AJNR Am J Neuroradiol,* 29(5), 913-918.

Petrovic, P., Kalso, E., Petersson, K.M., & Ingvar, M. (2002). Placebo and opioid analgesia--imaging a shared neuronal network. *Science, 295*(5560), 1737-1740.

Petzke, F., & Clauw, D.J. (2000). Sympathetic nervous system function in fibromyalgia. *Curr Rheumatol Rep, 2*(2), 116-123.

Peyron, R., Laurent, B., & García-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta-analysis. *Neurophysiol Clin, 30*(5), 263-288.

Pezet, S., & McMahon, S.B.(2006). Neurotrophins: mediators and modulators of pain.*Annu Rev Neurosci, 29*, 507-538.

Phillips, J. M. & Gatchel, R. J. (2000). Extraversion-introversion and chronic pain. Locus of control in the patient with chronic pain. In R. Gatchel & J. Weisberg (eds.) *Personality*

characteristics of patients with pain (pp. 181-202). Washington, DC: American Psychological Association.

Phillips, K., & Clauw, D.J. (2013). Central pain mechanisms in the rheumatic diseases: future directions. *Arthritis Rheum, 65*(2), 291-302.

Ploghaus, A., Tracey, I., Gati, J.S., Clare, S., Menon, R.S., Matthews, P.M., & Rawlins, J.N. (1999). Dissociating pain from its anticipation in the human brain. *Science, 284*(5422), 1979-1981.

Ploghaus, A., Narain, C., Beckmann, C.F., Clare, S., Bantick, S., Wise, R., Matthews, P.M., Rawlins, J.N., & Tracey, I. (2001). Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *J Neurosci, 21*(24), 9896-9903.

Pollatos, O., Matthias, E., & Keller, J. (2015). When interoception helps to overcome negative feelings caused by social exclusion, *Front Psychol, 6*, 786.

Pongratz, D.E., & Späth, M. Z. (1998). Morphologic aspects of fibromyalgia. *Rheumatol, 57*, 47-51.

Porreca, F., Ossipov, M.H., & Gebhart, G.F. (2002). Chronic pain and medullary descending facilitation.*Trends Neurosci, 25*(6), 319-325.

Price, D.D., Milling, L.S., Kirsch, I., Duff, A., Montgomery, G.H., & Nicholls, S.S. (1999). An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain, 83*(2), 147-156.

Price, D. (2000). Psychological and neural mechanisms of the affective dimension of pain. *Science, 288*, 1769-1772.

Pud, D., Granovsky, Y., & Yarnitsky, D. (2009). The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. *Pain, 144*(1-2), 16-9.

Pujol, J., López-Solà, M., Ortiz, H., Vilanova, J.C., Harrison, B.J., Yücel, M., Soriano-Mas, C., Cardoner, N., & Deus, J. (2009). Mapping brain response to pain in fibromyalgia patients using temporal analysis of FMRI. *PLoS One, 4*(4), e5224.

Queiroz, L.P. (2013). Worldwide epidemiology of fibromyalgia. *Curr Pain Headache Rep, 17*(8), 356.

Raczka, K.A., Gartmann, N., Mechias, M.L., Reif, A., Büchel, C., Deckert, J., & Kalisch, R. (2010). A neuropeptide S receptor variant associated with overinterpretation of fear reactions: a potential neurogenetic basis for catastrophizing. *Mol Psychiatry, 15*(11), 1067-1074.

Rainville, P., Duncan, G.H., Price, D.D., Carrier, B., & Bushnell, M.C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science, 277*(5328), 968-971.

Ramírez, M., Martínez-Martínez, L.A., Hernández-Quintela, E., Velazco-Casapía, J., Vargas, A., & Martínez-Lavín, M. (2015). Small fiber neuropathy in women with fibromyalgia. An in vivo assessment using corneal confocal bio-microscopy. *Semin Arthritis Rheum, 45*(2), 214-249.

Ramsey, I.S., Delling, M., & Clapham, D.E. (2006). An introduction to TRP channels. *Annu Rev Physiol, 68*, 619-647.

Reynolds, D.V. (1969). Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science, 164*(3878), 444-445.

Rhudy, J.L., DelVentura, J.L., Terry, E.L., Bartley, E.J., Olech, E., Palit, S., Kerr, K.L. (2013). Emotional modulation of pain and spinal nociception in fibromyalgia. *Pain, 154*, 1045-1056.

Riva, P., Williams, K.D., & Gallucci, M. (2014). The relationship between fear of social and physical threat and its effect on social distress and physical pain perception. *Pain, 155*, 485-493.

Riva, R., Mork, P.J., Westgaard, R.H., Rø, M., & Lundberg, U. (2010). Fibromyalgia syndrome is associated with hypocortisolism. *Int J Behav Med, 17*(3), 223-233.

Rohleder, N. (2014). Stimulation of systemic low-grade inflammation by psychosocial stress. *Psychosom Med, 76*(3), 181-189.

Rosado, M., Pereira, J., Fonseca, J., & Branco, J. (2006). Adaptação cultural e validação do "FibromyalgiaImpactQuestionnaire" – versão portuguesa. *Acta Reuma Port* 31, 157–165.

Roy, M., Peretz, I., & Rainville, P. (2008). Emotional valence contributes to music-induced analgesia. *Pain, 134*(1-2), 140-147.

Russell, I., Vaeroy, H., Javors, M., & Nyberg, F. (1992). Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. *Arthritis Rheum, 35*, 550-556.

Russell, I., & Littman, B. (1994). Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthristis Rheum, 37*, 1593-1601.

Russell, I.J. (2002). The promise of substance P inhibitors in fibromyalgia. *Rheum Dis Clin North Am, 28*(2), 329-342.

Santello, M., & Nevian, T. (2015). Dysfunction of cortical dendritic integration in neuropathic pain reversed by serotoninergic neuromodulation. *Neuron, 86*(1), 233-246.

Santos, R.A., Reis, P., Rebelo, L, Costa Dias, F., Miranda Rosa, C., & Viana Queiroz, M. (1996). Health Assessment Questionnaire (versão curta). Adaptação para a Língua Portuguesa e Estudo da sua Aplicabilidade. *Acta Reuma Port, 76*, 15-20.

Schmidt-Wilcke, T., Leinisch, E., Straube, A., Kämpfe, N., Draganski, B., Diener, H.C., Bogdahn, U., & May, A. (2005). Gray matter decrease in patients with chronic tension type headache. *Neurology, 65*(9), 1483-1486.

Schmidt-Wilcke, T., Luerding, R., Weigand, T., Jürgens, T., Schuierer, G., Leinisch, E., & Bogdahn, U. (2007). Striatal grey matter increase in patients suffering from fibromyalgia--a voxel-based morphometry study. *Pain, 132*, S109-116.

Schmidt-Wilcke, T. (2008). Variations in brain volume and regional morphology associated with chronic pain. *Curr Rheumatol Rep, 10*(6), 467-474.

Schwartz, N., Temkin, P., Jurado, S., Lim, B.K., Heifets, B.D., Polepalli, J.S., & Malenka, R.C. (2014). Decreased motivation during chronic pain requires long-term depression in the nucleus accumbens. *Science, 345*(6196), 535-542.

Schweinhardt, P., Kalk, N., Wartolowska, K., Chessell, I., Wordsworth, P., & Tracey, I. (2008). Investigation into the neural correlates of emotional augmentation of clinical pain. *Neuroimage, 40*(2), 759-766.

Schweinhardt, P., Seminowicz, D.A., Jaeger, E., Duncan, G.H., & Bushnell, M.C. (2009). The anatomy of the mesolimbic reward system: a link between personality and the placebo analgesic response. *J Neurosci, 29*(15), 4882-4887.

Scott D.J., Stohler, C.S., Egnatuk, C.M., Wang, H., Koeppe, R.A., & Zubieta, J.K. (2008). Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry, 65*(2), 220-231.

Sebastian, C.L., Tan, G.C., Roiser, J.P., Viding, E., Dumontheil, I., & Blakemore, S.J. (2011). Developmental influences on the neural bases of responses to social rejection: implications of social neuroscience for education. *Neuroimage, 57*(3), 686-94.

Seidel, E.M., Silani, G., Metzler, H., Thaler, H., Lamm, C., Gur, R.C., Kryspin-Exner, I., Habel, U., & Derntl, B. (2013). The impact of social exclusion vs. inclusion on subjective and hormonal reactions in females and males. *Psychoneuroendocrinology, 38*(12), 2925-2932.

Seminowicz, D.A., & Davis, K.D. (2006). Cortical responses to pain in healthy individuals depends on pain catastrophizing. *Pain, 120*(3), 297-306.

Seminowicz, D.A., & Davis, K.D. (2007). Interactions of pain intensity and cognitive load: the brain stays on task. *Cereb Cortex, 17(*6), 1412-1422.

Sherrington, C.S. (1947). *The integrative action of the nervous system.* New Haven, CT: Yale University Press.

Silvestrini, N., & Rainville, P. (2013). After-effects of cognitive control on pain. *Eur J Pain, 17*(8), 1225-1233.

Simms, R.W. (1998). Fibromyalgia is not a muscle disorder. *Am J Med Sci, 315*(6), 346-350.

Slavich, G.M., O'Donovan, A., Epel, E.S., & Kemeny, M.E. (2010). Black sheep get the blues: a psychobiological model of social rejection and depression. *NeurosciBiobehav Rev* 35, 39-45.

Sotres-Bayón, F., Torres-López, E., López-Avila, A., del Angel, R., & Pellicer, F. (2001). Lesion and electrical stimulation of the ventral tegmental area modify persistent nociceptive behavior in the rat. *Brain Res, 898*(2), 342-349.

Sprott, H., Salemi, S., Gay, R., Bradley, L., Alarcon, G., Michel, B., & Gay, S. (2004). Increased DNA fragmentation and ultrastructural changes in fibromyalgic muscle fibres. *Ann Rheum Dis, 63*, 245-251.

Spunt, R.P., Lieberman, M.D., Cohen, J.R., & Eisenberger, N.I. (2012). The phenomenology of error processing: the dorsal ACC response to stop-signal errors tracks reports of negative affect. *J Cogn Neurosci, 24*(8), 1753-1765.

Staud, R., Cannon, R.C., Mauderli, A.P., Robinson, M.E., Price, D.D., & Vierck, C.J. Jr. (2003). Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. *Pain, 102*, 87-95.

Staud, R. (2006a). Biology and therapy of fibromyalgia: pain in fibromyalgia syndrome. *Arthritis Res Ther, 8*(3), 208.

Staud, R., Price, D.D., & Fillingim, R.B. (2006b). Advanced continuous-contact heat pulse design for efficient temporal summation of second pain (windup). *J Pain, 7*(8), 575-582.

Staud, R., Robinson, M.E., & Price, D.D. (2007). Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. *J Pain 8*,893-901.

Staud, R., Craggs, J.G., Perlstein, W.M., Robinson, M.E., & Price, D.D. (2008). Brain activity associated with slow temporal summation of C-fiber evoked pain in fibromyalgia patients and healthy controls. *Eur J Pain, 12*(8), 1078-1089.

Staud, R., Nagel, S., Robinson, M.E., & Price, D.D. (2009). Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: a randomized, double-blind, placebo-controlled study. *Pain, 145*(1-2), 96-104.

Stucky, C.L., Dubin, A.E., Jeske, N.A., Malin, S.A., McKemy, D.D., & Story, G.M. (2009). Roles of transient receptor potential channels in pain. *Brain Res Rev, 60*(1), 2-23.

Sundermann, B., Burgmer, M., Pogatzki-Zahn, E., Gaubitz, M., Stüber, C., Wessolleck, E., Heuft, G., & Pfleiderer, B. (2014). Diagnostic classification based on functional connectivity in chronic pain: model optimization in fibromyalgia and rheumatoid arthritis. *Acad Radiol, 21*(3), 369-377.

Sundgren, P.C., Petrou, M., Harris, R.E., Fan, X., Foerster, B., Mehrotra, N., Sen, A., Clauw, D.J., & Welsh, R.C. (2007). Diffusion-weighted and diffusion tensor imaging in fibromyalgia patients: a prospective study of whole brain diffusivity, apparent diffusion coefficient, and fraction anisotropy in different regions of the brain and correlation with symptom severity. *Acad Radiol, 14*(7), 839-846.

Tak, L.M., Riese, H., de Bock, G.H., Manoharan, A., Kok, I.C., & Rosmalen, J.G. (2009). As good as it gets? A meta-analysis and systematic review of methodological quality of heart rate variability studies in functional somatic disorders. *Biol Psychol, 82*(2), 101-110.

Tang, N.K., Salkovskis, P.M., Hodges, A., Wright, K.J., Hanna, M., & Hester, J. (2008). Effects of mood on pain responses and pain tolerance: an experimental study in chronic back pain patients. *Pain, 138*(2), 392-401.

Taniguchi, W., Nakatsuka, T., Miyazaki, N., Yamada, H., Takeda, D., Fujita, T., Kumamoto, E., & Yoshida, M. (2011). In vivo patch-clamp analysis of dopaminergic antinociceptive actions on substantia gelatinosa neurons in the spinal cord. *Pain, 152*(1), 95-105.

Tanriverdi, F., Karaca, Z., Unluhizarci, K., & Kelestimur, F. (2007). The hypothalamo-pituitary-adrenal axis in chronic fatigue syndrome and fibromyalgia syndrome. *Stress*, *10*(1), 13-25.

Tidey, J.W., & Miczek, K.A. (1996). Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. *Brain Res, 721*(1-2), 140-149.

Todd, A.J. (2010). Neuronal circuitry for pain processing in the dorsal horn. *Nat Rev Neurosci, 11*(12), 823-836.

Tracey, I., Ploghaus, A., Gati, J.S., Clare, S., Smith, S., Menon, R.S., & Matthews, P.M. (2002). Imaging attentional modulation of pain in the periaqueductal gray in humans. *J Neurosci, 22*(7), 2748-2752.

Tracey, I., & Mantyh, P.W.(2007). The cerebral signature for pain perception and its modulation. *Neuron, 55*, 377–391.

Tracey, I., & Bushnell, M.C. (2009). How neuroimaging studies have challenged us to rethink: is chronic pain a disease? *J. Pain, 10*, 1113-1120.

Tracey, I. (2011). Can neuroimaging studies identify pain endophenotypes in humans? *Nat Rev Neurol, 7*(3), 173-181.

Treister, R., Pud, D., & Eisenberg, E. (2013). The dopamine agonist apomorphine enhances conditioned pain modulation in healthy humans. *Neurosci Lett* 548, 115-9.

Treister, R., Nielsen, C.S., Stubhaug, A., Farrar, J.T., Pud, D., Sawilowsky, S., & Oaklander, A.L. (2015). Experimental comparison of parametric versus nonparametric analyses of data from the cold pressor test. *J Pain 16*,537-48.

Trief, P.M., Elliott, D.J., Stein, N., & Frederickson, B.E. (1987). Functional vs. organic pain: a meaningful distinction? *J Clin Psychol, 43*(2), 219-226.

Twenge, J.M., Baumeister, R.F., Tice, D.M., & Stucke, T.S. (2001). If you can't join them, beat them: Effects of social exclusion on aggressive behavior. *J Pers Soc Psychol, 81*, 1058-1069.

Uchino, B.N., Cacioppo, J.T., & Kiecolt-Glaser, J.K. (1996). The relationship between social support and physiological processes: A review with emphasis on underlying mechanisms and implications for health. *Psychological Bulletin*, *119*, 488-531.

Valdés, M., Collado, A., Bargalló, N., Vázquez, M., Rami, L., Gómez, E., & Salamero, M. (2010). Increased glutamate/glutamine compounds in the brains of patients with fibromyalgia: a magnetic resonance spectroscopy study. *Arthritis Rheum, 62*(6), 1829-1836.

Valet, M., Sprenger, T., Boecker, H., Willoch, F., Rummeny, E., Conrad, B., Erhard, P., & Tolle, T.R. (2004). Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain--an fMRI analysis. *Pain, 109*(3), 399-408.

van Noordt, S.J., White, L.O., Wu, J., Mayes, L.C., & Crowley, M.J. (2015). Social exclusion modulates event-related frontal theta and tracks ostracism distress in children. *Neuroimage, 118*, 248-255.

van Rossum, E.F., Binder, E.B., Majer, M., Koper, J.W., Ising, M., Modell, S., Salyakina, D., Lamberts, S.W., & Holsboer, F. (2006). Polymorphisms of the glucocorticoid receptor gene and major depression. *Biol Psychiatry, 59*(8), 681-688.

van Wijk, G., & Veldhuijzen, D.S.(2010). Perspective on diffuse noxious inhibitory controls as a model of endogenous pain modulation in clinical pain syndromes. *J Pain, 11*(5), 408-419.

Vase, L., Robinson, M.E., Verne, G.N., & Price, D.D. (2005). Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *Pain, 115*(3), 338-347.

Vidal, C., & Jacob, J. (1986). Hyperalgesia induced by emotional stress in the rat: an experimental animal model of human anxiogenic hyperalgesia. *Ann N Y Acad Sci, 467*, 73-81.

Vierck, C.J. Jr. (2006). Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). *Pain, 124*,242-63.

Viguier, F., Michot, B., Hamon, M., & Bourgoin, S. (2013). Multiple roles of serotonin in pain control mechanisms--implications of 5-HT$_7$ and other 5-HT receptor types. *Eur J Pharmacol, 716* (1-3), 8-16.

Villemure, C., Slotnick, B.M., & Bushnell, M.C. (2003). Effects of odors on pain perception: deciphering the roles of emotion and attention. *Pain, 106*(1-2), 101-108.

Vincent, A., Lahr, B.D., Wolfe, F., Clauw, D.J., Whipple, M.O., Oh, T.H., Barton, D.L., & St Sauver, J. (2013). Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. *Arthritis Care Res, 65*(5), 786-792.

Vohs, K.D., Baumeister, R.F., Schmeichel, B.J., Twenge, J.M., Nelson, N.M., & Tice, D.M. (2008). Making choices impairs subsequent self-control: a limited-resource account of decision making, self-regulation, and active initiative. *J Pers Soc Psychol, 94*(5), 883-898.

Wager, T.D., Matre, D., & Casey, K.L. (2006). Placebo effects in laser-evoked pain potentials. *Brain Behav Immun, 20(*3), 219-230.

Wager, T.D., Rilling, J.K., Smith, E.E., Sokolik, A., Casey, K.L., Davidson, R.J., Kosslyn, S.M., Rose, R.M., & Cohen, J.D. (2004). Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science, 303*(5661), 1162-1167.

Wai, M.S., Lorke, D.E., Kwong, W.H., Zhang, L., & Yew, D.T. (2011). Profiles of serotonin receptors in the developing human thalamus. *Psychiatry Res, 185*(1-2), 238-242.

Walker, E.A., Keegan, D., Gardner, G., Sullivan, M., Katon, W.J., & Bernstein, D. (1997). Psychosocial factors in fibromyalgia compared with rheumatoid arthritis: I. Psychiatric diagnoses and functional disability. *Psychosom Med, 59*(6), 565-571.

Walteros, C., Sánchez-Navarro, J.P., Muñoz, M.A., Martínez-Selva, J.M., Chialvo, D., & Montoya, P. (2011). Altered associative learning and emotional decision making in fibromyalgia. *J Psychosom Res, 70*(3), 294-301.

Ware, J. Jr., & Sherbourne, C.D. (1992). The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual Framework and Item Selection. *Medical Care, 30*, 473-483.

Watkins, L.R., Milligan, E.D., & Maier, S.F. (2001). Glial activation: a driving force for pathological pain. *Trends Neurosci, 24*(8), 450-455.

Webster, M.J., Knable, M.B., O'Grady, J., Orthmann, J., & Weickert, C.S.(2002). Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. *Mol Psychiatry, 7*(9), 985-994.

Wei, H., Viisanen, H., & Pertovaara, A. (2009). Descending modulation of neuropathic hypersensitivity by dopamine D2 receptors in or adjacent to the hypothalamic A11 cell group. *Pharmacol Res, 59*(5), 355-363.

Weik, U., Maroof, P., Zöller, C., & Deinzer, R. (2010). Pre-experience of social exclusion suppresses cortisol response to psychosocial stress in women but not in men. *Horm Behav, 58*(5), 891-897.

Weik, U., Kuepper, Y., Hennig, J., & Deinzer, R. (2013). Effects of pre-experience of social exclusion on hypothalamus-pituitary-adrenal axis and catecholaminergic responsiveness to public speaking stress. *PLoS One, 8*(4), e60433.

Weissbecker, I., Floyd, A., Dedert, E., Salmon, P., & Sephton, S. (2006). Childhood trauma and diurnal cortisol disruption in fibromyalgia syndrome. *Psychoneuroendocrinology, 31*(3), 312-324.

Wendler, J., Hummel, T., Reissinger, M., Manger, B., Pauli, E., Kalden, J.R., & Kobal, G. (2001). Patients with rheumatoid arthritis adapt differently to repetitive painful stimuli compared to healthy controls. *J Clin Neurosci, 8*(3), 272-277.

Weschke, S., & Niedeggen, M. (2013). The effect of the physical presence of co-players on perceived ostracism and event-related brain potentials in the cyberball paradigm. *PLoS One, 8*(8), e71928.

Westermann, S., Rief, W., Euteneuer, F., & Kohlmann, S. (2015). Social exclusion and shame in obesity. *Eat Behav, 17*, 74-76.

White, L.O., Wu, J., Borelli, J.L., Mayes, L.C., & Crowley, M.J.(2013). Play it again: neural responses to reunion with excluders predicted by attachment patterns. *Dev Sci, 16*(6), 850-863.

Wiech, K., Kalisch, R., Weiskopf, N., Pleger, B., Stephan, K.E., & Dolan, R.J.(2006). Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. *J Neurosci, 26*(44), 11501-11509.

Wiech, K., & Tracey, I. (2009). The influence of negative emotions on pain: Behavioral effects and neural mechanisms. *Neuroimage, 47*, 987-994.

Wieseler-Frank, J., Maier, S.F., & Watkins, L.R. (2005). Immune-to-brain communication dynamically modulates pain: physiological and pathological consequences. *Brain Behav Immun, 19*(2), 104-111.

Williams, D.A., & Clauw, D.J. (2009). Understanding fibromyalgia: lessons from the broader pain research community. *J Pain 10*, 777-791.

Williams, D.A., & Schilling, S. (2009). Advances in the assessment of fibromyalgia. *Rheum Dis Clin North Am,35*(2), 339-357.

Williams, K.D., Cheung, C.K.T., & Choi, W. (2000). Cyberostracism: Effects of Being Ignored Over the Internet. *J Pers Soc Psychol, 79*, 748-762.

Wingenfeld, K., Nutzinger, D., Kauth, J., Hellhammer, D.H., & Lautenbacher, S. (2010). Salivary cortisol release and hypothalamic pituitary adrenal axis feedback sensitivity in fibromyalgia is associated with depression but not with pain. *J Pain, 11*(11), 1195-1202.

Witting, N., Kupers, R.C., Svensson, P., & Jensen, T.S. (2006). A PET activation study of brush-evoked allodynia in patients with nerve injury pain. *Pain, 120*(1-2), 145-154.

Wolfe, F., Smythe, H. A., Yunus, M.B., Bennett, R.M., Bombardier, C., Goldenberg, D.L., Tugwell, P., Campbell, S.M., Abeles, M., Clark, P., et al. (1990). The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: Report of the Multicenter Criteria Committee. *Arthritis and Rheumatism, 33*, 2, 160-172.

Wolfe, F. (1997). The relation between tender points and fibromyalgia symptom variables: evidence that fibromyalgia is not a discrete disorder in the clinic. *Ann Rheum Dis, 56*(4), 268-271.

Wolfe, F., Clauw D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P, Russell, A. S.,Russell, I. J., Winfield, J. B., & Yunus, M.B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res, 62,* 600–10.

Wolfe, F., Brähler, E., Hinz, A., & Häuser, W. (2013). Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. *Arthritis Care Res, 65*(5), 777-785.

Woo, C.W., Koban, L., Kross, E., Lindquist, M.A., Banich, M.T., Ruzic, L., Andrews-Hanna, J.R., & Wager, T.D. (2014). Separate neural representations for physical pain and social rejection. *Nat Commun, 5380*, 1-12.

Wood, P.B., Schweinhardt, P., Jaeger, E., Dagher, A., Hakyemez, H., Rabiner, E.A., Bushnell, M.C., & Chizh, B.A. (2007). Fibromyalgia patients show an abnormal dopamine response to pain. *Eur J Neurosci, 25*, 3576-82.

Wood, P.B., Glabus, M.F., Simpson, R., & Patterson, J.C. 2nd (2009). Changes in gray matter density in fibromyalgia: correlation with dopamine metabolism. *J Pain, 10*(6), 609-618.

Woolf, C.J., & Salter, M.W. (2000). Neuronal plasticity: increasing the gain in pain. *Science, 288*(5472), 1765-1769.

Woolf, C.J., & Ma, Q. (2007). Nociceptors--noxious stimulus detectors. *Neuron, 55*(3), 353-364.

Yang, H.W., Zhou, L.J., Hu, N.W., Xin, W.J., & Liu, X.G. (2005). Activation of spinal d1/d5 receptors induces late-phase LTP of C-fiber-evoked field potentials in rat spinal dorsal horn. *J Neurophysiol, 94*(2), 961-967.

Yang, Y.C., Schorpp, K., & Harris, K.M. (2014). Social support, social strain and inflammation: evidence from a national longitudinal study of U.S. adults. *Soc Sci Med, 107*, 124-135.

Yarnitsky, D. (2010). Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol, 23*(5), 611-615.

Yin, J.B., Wu, H.H., Dong, Y.L., Zhang, T., Wang, J., Zhang, Y., Wei, Y.Y., Lu, Y.C., Wu, S.X., Wang, W., & Li, Y.Q. (2014). Neurochemical properties of BDNF-containing neurons projecting to rostral ventromedial medulla in the ventrolateral periaqueductal gray. *Front Neural Circuits, 8*, 137.

Yoshino, A., Okamoto, Y., Onoda, K., Yoshimura, S., Kunisato, Y., Demoto, Y., Okada, G., & Yamawaki, S. (2010). Sadness enhances the experience of pain via neural activation in the anterior cingulate cortex and amygdala: an fMRI study. *Neuroimage, 50*, 1194-1201.

Yunus, M.B., Kalyan-Raman, U.P., & Kalyan-Raman, K. (1988). Primary fibromyalgia syndrome and myofascial pain syndrome: clinical features and muscle pathology. *Arch Phys Med Rehabil, 69*(6), 451-454.

Yunus, M.B. (2007). Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. *Semin Arthritis Rheum, 36*(6), 339-356.

Yunus, M.B. (2008). Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. *Semin Arthritis Rheum, 37*, 339-352.

Yunus, M.B. (2015). Editorial review: an update on central sensitivity syndromes and the issues of nosology and psychobiology. *Curr Rheumatol Rev, 11*(2), 70-85.

Zambito Marsala, S., Pistacchi, M., Tocco, P., Gioulis, M., Fabris, F., Brigo, F., & Tinazzi, M. (2015). Pain perception in major depressive disorder: A neurophysiological case-control study. *J Neurol Sci, 357*(1-2), 19-21.

Zautra, A.J., Fasman, R., Reich, J.W., Harakas, P., Johnson, L.M., Olmsted, M.E., & Davis, M.C. (2005). Fibromyalgia: evidence for deficits in positive affect regulation. *Psychosom Med, 67*(1), 147-155.

Zigmond, A.S., & Snaith, R.P. (1983). The Hospital and Anxiety Depression Scale. *Acta Psychiatr Scand,* 7, 361-370.

Zubieta, J.K., Bueller, J.A., Jackson, L.R., Scott, D.J., Xu, Y., Koeppe, R.A., Nichols, T.E., & Stohler, C.S. (2005). Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *J Neurosci, 25*(34), 7754-7762.

APPENDICES

1. QUESTIONNAIRES

EXPERIÊNCIAS EM RELAÇÕES PRÓXIMAS

Brennan et al. (1998); Versão Portuguesa Moreira et al. (2006)

Por favor, leia cada uma das seguintes afirmações e avalie o grau em que cada uma delas descreve os seus sentimentos acerca das relações com os seus parceiros/as (p. ex., marido/mulher, namorado/a, companheiro/a, etc). Pense em todas as suas relações, passadas e presentes, e responda em termos de como geralmente se sente nessas relações. Responda a cada afirmação indicando o quanto concorda ou discorda. Assinale o número correspondente à sua resposta, utilizando a seguinte escala:

Discordo fortemente — Neutro/misto — Concordo fortemente

1 2 3 4 5 6 7

	1	2	3	4	5	6	7
1. Prefiro não mostrar ao meu parceiro/a como me sinto lá no fundo.	❍	❍	❍	❍	❍	❍	❍
2. Preocupa-me o ser abandonado/a.	❍	❍	❍	❍	❍	❍	❍
3. Sinto-me muito confortável em estar próximo/a dos meus parceiros/as.	❍	❍	❍	❍	❍	❍	❍
4. Preocupo-me muito com as minhas relações afectivas.	❍	❍	❍	❍	❍	❍	❍
5. Quando o meu parceiro/a começa a aproximar-se emocionalmente de mim, tendo a afastar-me.	❍	❍	❍	❍	❍	❍	❍
6. Preocupa-me que os meus parceiros/as não se preocupem tanto comigo como eu com eles/elas.	❍	❍	❍	❍	❍	❍	❍
7. Sinto-me desconfortável quando um/a parceiro/a quer ser muito próximo/a.	❍	❍	❍	❍	❍	❍	❍
8. Preocupo-me bastante com a possibilidade de perder o meu parceiro/a.	❍	❍	❍	❍	❍	❍	❍
	❍	❍	❍	❍	❍	❍	❍

9. Não me sinto confortável ao "abrir-me" com os meus parceiros/as.							
10. Desejo muitas vezes que os sentimentos do meu parceiro/a por mim sejam tão fortes como os meus por ele/ela.	❍	❍	❍	❍	❍	❍	❍
11. Quero tornar-me próxima do meu parceiro/a mas estou sempre a afastar-me.	❍	❍	❍	❍	❍	❍	❍
12. Quero muitas vezes unir-me completamente aos meus parceiros/as e isso, por vezes, afasta-os/as.	❍	❍	❍	❍	❍	❍	❍
13. Fico nervoso/a quando os meus parceiros/as se tornam demasiado próximos.	❍	❍	❍	❍	❍	❍	❍
14. Preocupa-me o estar sozinho/a.	❍	❍	❍	❍	❍	❍	❍
15. Sinto-me confortável ao partilhar os meus pensamentos e sentimentos íntimos com o meu parceiro/a.	❍	❍	❍	❍	❍	❍	❍
16. O meu desejo de me tornar muito próximo/a por vezes assusta as pessoas.	❍	❍	❍	❍	❍	❍	❍
17. Tento evitar tornar-me demasiado próximo/a do meu parceiro/a.	❍	❍	❍	❍	❍	❍	❍
18. Preciso de muitas manifestações de amor para me sentir amado/a pelo meu parceiro/a.	❍	❍	❍	❍	❍	❍	❍
19. Sinto que é relativamente fácil tornar-me próximo/a do meu parceiro/a.	❍	❍	❍	❍	❍	❍	❍
20. Às vezes sinto que pressiono os meus parceiros/as para mostrarem mais sentimento e mais empenho.	❍	❍	❍	❍	❍	❍	❍
21. Sinto dificuldade em permitir a mim mesmo/a apoiar-me nos meus parceiros/as.	❍	❍	❍	❍	❍	❍	❍
22. Não me preocupo muitas vezes	❍	❍	❍	❍	❍	❍	❍

com o ser abandonado/a.							
23. Prefiro não ser muito próximo/a dos meus parceiros/as.	❍	❍	❍	❍	❍	❍	❍
24. Se não consigo que o meu parceiro/a mostre interesse por mim, fico perturbado/a ou zangado/a.	❍	❍	❍	❍	❍	❍	❍
25. Conto praticamente tudo ao meu parceiro/a.	❍	❍	❍	❍	❍	❍	❍
26. Penso que o meu parceiro/a não se quer tornar tão próximo/a como eu gostaria.	❍	❍	❍	❍	❍	❍	❍
27. Costumo discutir os meus problemas e preocupações com o meu parceiro/a.	❍	❍	❍	❍	❍	❍	❍
28. Quando não estou envolvido/a numa relação, sinto-me um pouco ansioso/a e inseguro/a.	❍	❍	❍	❍	❍	❍	❍
29. Sinto-me confortável ao apoiar-me nos meus parceiros/as.	❍	❍	❍	❍	❍	❍	❍
30. Fico frustrado/a quando o meu parceiro/a não está comigo tanto tempo como eu gostaria.	❍	❍	❍	❍	❍	❍	❍
31. Não me importo de pedir aos meus parceiros/as conforto, conselhos ou ajuda.	❍	❍	❍	❍	❍	❍	❍
32. Fico frustrado/a se os meus parceiros/as não estão disponíveis quando eu preciso deles/delas.	❍	❍	❍	❍	❍	❍	❍
33. Ajuda-me poder contar com o meu parceiro/a nas situações de necessidade.	❍	❍	❍	❍	❍	❍	❍
34. Quando os meus parceiros/as me desaprovam, sinto-me muito mal comigo mesmo/a.	❍	❍	❍	❍	❍	❍	❍
35. Recorro ao meu parceiro/a para muitas coisas, incluindo conforto e segurança.	❍	❍	❍	❍	❍	❍	❍
	❍	❍	❍	❍	❍	❍	❍

36. Fico ressentido/a quando o meu parceiro/a passa tempo longe de mim.							

INVENTÁRIO BIG FIVE

John & Srivastava (1999); Versão Portuguesa João M. Moreira (2006)

Aqui estão algumas características que podem ou não aplicar-se a si. Por exemplo, você concorda que é alguém que gosta de passar tempo com outras pessoas? Por favor escreva um número junto a cada afirmação para indicar até que ponto concorda ou discorda com essa afirmação.

1 = Discordo fortemente

2 = Discordo um pouco

3 = Não concordo nem discordo

4 = Concordo um pouco

5 = Concordo fortemente

Vejo-me como alguém que…

	1 - Discordo fortemente	2 - Discordo um pouco	3 - Não concordo nem discordo	4 - Concordo um pouco	5 - Concordo fortemente
1. É deprimido, triste.	❍	❍	❍	❍	❍
2. É calmo, lida bem com o stress.	❍	❍	❍	❍	❍
3. Pode ser tenso.	❍	❍	❍	❍	❍
4. Se preocupa muito.	❍	❍	❍	❍	❍
5. É emocionalmente estável, não se perturba facilmente.	❍	❍	❍	❍	❍
6. Permanece calmo em situações tensas.	❍	❍	❍	❍	❍
7. Fica nervoso facilmente	❍	❍	❍	❍	❍

QUESTIONÁRIO DE ESTADO DE SAÚDE SF36

Ware & Sherbourne (1992); Versão Portuguesa Pais-Ribeiro (2005)

As questões que se seguem pedem-lhe opinião sobre a sua saúde, a forma como se sente e sobre a sua capacidade de desempenhar as actividades habituais. Pedimos que leia com atenção cada pergunta e que responda o mais honestamente possível. Se não tiver a certeza sobre a resposta a dar, dê-nos a que achar mais apropriada.

1. Em geral, diria que a sua saúde é:

- ❍ Óptima
- ❍ Muito boa
- ❍ Boa
- ❍ Razoável
- ❍ Fraca

2. Comparando com o que acontecia há uma semana, como descreve o seu estado geral actual:

- ❍ Muito melhor
- ❍ Com algumas melhoras
- ❍ Aproximadamente igual
- ❍ Um pouco pior
- ❍ Muito pior

3. As perguntas que se seguem são sobre actividades que executa no seu dia-a-dia. Será que a sua saúde o/a limita nestas actividades? Se sim quanto?

	Sim, muito limitado/a	Sim, um pouco limitado/a	Não, nada limitado/a
a. Actividades violentas, tais como correr, levantar pesos, participar em desportos violentos.	❍	❍	❍
b. Actividades moderadas, tais como deslocar uma mesa, aspirar a casa, jogar bowling ou jogar golfe.	❍	❍	❍
c. Levantar ou carregar as compras de mercearia.	❍	❍	❍
d. Subir vários lanços de escadas.	❍	❍	❍
e. Subir um lanço de escadas.	❍	❍	❍
f. Inclinar-se, ajoelhar-se ou baixar-se	❍	❍	❍
g. Andar mais de 1 km.	❍	❍	❍
h. Andar vários quarteirões.	❍	❍	❍
i. Andar um quarteirão.	❍	❍	❍
j. Tomar banho ou vestir-se sozinho/a.	❍	❍	❍

4. Durante a última semana, teve no seu trabalho ou actividades diárias algum dos problemas apresentados a seguir como consequência do seu estado de saúde físico?

	Sim	Não
k. Diminuiu o tempo gasto a trabalhar, ou noutras actividades.	❍	❍
l. Fez menos do que queria.	❍	❍
m. Sentiu-se limitado/a no tipo de trabalho ou noutras actividades.	❍	❍
n. Teve dificuldade em executar o seu trabalho ou outras actividades (por exemplo, foi preciso mais esforço).	❍	❍

5. Durante a última semana, teve com o seu trabalho ou com as suas actividades diárias, algum dos problemas apresentados a seguir devido a quaisquer problemas emocionais (tal como sentir-se deprimido/a ou ansioso/a)?

	Sim	Não
o. Diminuiu o tempo gasto a trabalhar, ou noutras actividades.	❍	❍
p. Fez menos do que queria.	❍	❍
q. Não executou o trabalho ou outras actividades tão cuidadosamente como era costume.	❍	❍

6. Durante a última semana, em que medida é que a sua saúde física ou problemas emocionais interferiram com o seu relacionamento social normal com a sua família, amigos, vizinhos ou outras pessoas?

- ❍ Absolutamente nada
- ❍ Pouco
- ❍ Moderadamente
- ❍ Bastante
- ❍ Imenso

7. Durante a última semana teve dores?

- ❍ Nenhumas
- ❍ Muito fracas
- ❍ Ligeiras
- ❍ Moderadas
- ❍ Fortes
- ❍ Muito fortes

8. Durante a última semana, de que forma é que a dor interferiu com o seu trabalho normal (tanto o trabalho fora de casa como o trabalho doméstico)?

- ❍ Absolutamente nada
- ❍ Um pouco
- ❍ Moderadamente
- ❍ Bastante
- ❍ Imenso

9. As perguntas que se seguem pretendem avaliar a forma como se sentiu e como lhe correram as coisas na última semana. Para cada pergunta, coloque por favor um círculo à volta do número que melhor descreva a forma como se sentiu. Quanto tempo, na última semana:

	Sempre	A maior parte do tempo	Bastante tempo	Algum tempo	Pouco tempo	Nunca
r. se sentiu cheio/a de vitalidade?	❍	❍	❍	❍	❍	❍
s. se sentiu muito nervoso/a?	❍	❍	❍	❍	❍	❍
t. se sentiu tão deprimido/a que nada o/a animava?	❍	❍	❍	❍	❍	❍
u. se sentiu calmo/a e tranquilo/a?	❍	❍	❍	❍	❍	❍
v. se sentiu com muita energia?	❍	❍	❍	❍	❍	❍
w. se sentiu triste e em baixo?	❍	❍	❍	❍	❍	❍
x. se sentiu estafado/a?	❍	❍	❍	❍	❍	❍
y. se sentiu feliz?	❍	❍	❍	❍	❍	❍
z. se sentiu cansado/a?	❍	❍	❍	❍	❍	❍

10. Durante a última semana, até que ponto é que a sua saúde física ou problemas emocionais limitaram a sua actividade social (tal como visitar amigos ou familiares próximos)?

- ❍ Sempre
- ❍ A maior parte do tempo
- ❍ Algum tempo
- ❍ Pouco tempo
- ❍ Nunca

11. Por favor, diga em que medida são VERDADEIRAS ou FALSAS as seguintes afirmações:

	Absolutamente verdade	Verdade	Não sei	Falso	Absolutamente falso
aa. Parece que adoeço mais facilmente do que os outros.	❍	❍	❍	❍	❍
bb. Sou tão saudável como qualquer outra pessoa.	❍	❍	❍	❍	❍
cc. Estou convencido/a que a minha saúde vai piorar.	❍	❍	❍	❍	❍
dd. A minha saúde é óptima.	❍	❍	❍	❍	❍

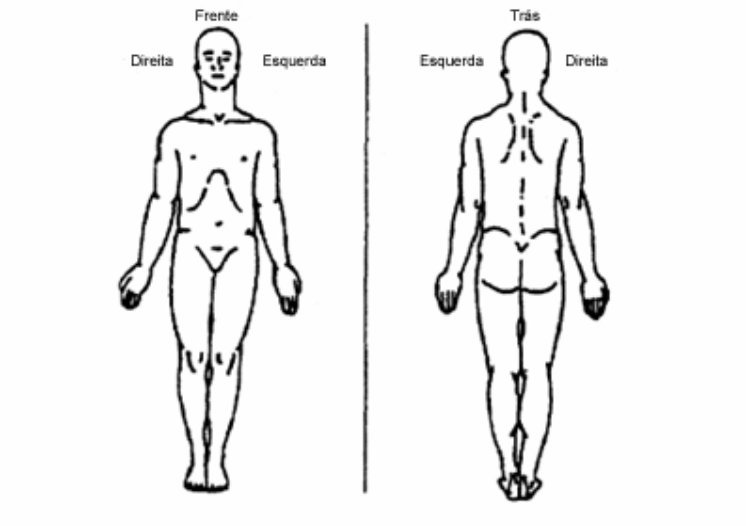
INVENTÁRIO RESUMIDO DA DOR (FORMULÁRIO ABREVIADO)

Cleeland & Ryan (1994), Versão Portuguesa Azevedo et al. (2007)

1. Ao longo da vida, a maior parte de nós teve dor de vez em quando (tais como dores de cabeça de pequena importância, entorses e dores de dentes). Durante a última semana teve alguma dor diferente destas dores comuns?

- ❍ Sim
- ❍ Não

2. Nas figuras clique nas áreas onde sente dor. Faça 3 cliques na zona que lhe dói mais.



3. Por favor, classifique a sua dor assinalando o número que melhor descreve a sua dor no seu **MÁXIMO** durante a última semana.

Sem dor										A pior dor que se pode imaginar
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

4. Por favor, classifique a sua dor assinalando o número que melhor descreve a sua dor no **MÍNIMO** durante a última semana.

Sem dor										A pior dor que se pode imaginar
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

5. Por favor, classifique a sua dor assinalando o número que melhor descreve a sua dor em **MÉDIA**.

Sem dor										A pior dor que se pode imaginar
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

6. Por favor, classifique a sua dor assinalando o número que indica a intensidade da sua dor **NESTE PRECISO MOMENTO**.

Sem dor										A pior dor que se pode imaginar
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

7. Que tratamentos ou medicamentos está a fazer para a sua dor?

_____
_____
_____

8. Na última semana, até que ponto é que os tratamentos e os medicamentos aliviaram a sua dor? Por favor, assinale com um círculo a percentagem que melhor demonstra o ALÍVIO que sentiu.

Nenhum alívio										Alívio completo
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
○	○	○	○	○	○	○	○	○	○	○

9. Assinale o número que descreve em que medida é que, durante a última semana, a sua dor interferiu com a sua/seu

	Não interferiu										Interferiu completamente
	0	1	2	3	4	5	6	7	8	9	10
Actividade geral	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Disposição	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Capacidade para andar a pé	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Trabalho normal (inclui tanto o trabalho doméstico como o trabalho fora de casa)	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Relações com outras pessoas	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Sono	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍
Prazer de viver	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍	❍

HADS

Zigmond & Snaith (1983); Versão Portuguesa MacIntyre et al. (1999)

Os profissionais de saúde sabem que as emoções desempenham um papel importante na maior parte das doenças. Se o seu profissional de saúde souber acerca destes sentimentos poderá ajudá-lo(a) melhor. Este questionário visa ajudar o seu profissional de saúde a saber como se sente. Leia cada frase e indique a resposta que mais se aproxima da forma como se tem sentido na última semana. Não passe muito tempo com cada resposta; a sua reacção imediata a cada uma das frases será provavelmente mais exacta do que uma resposta em que tenha pensado muito tempo.

Sinto-me tenso:	❍ A maior parte do tempo	❍ Muitas vezes	❍ De vez em quando, ocasionalmente	❍ Nunca
Ainda gosto das coisas de que costumava gostar:	❍ Tanto como gostava	❍ Não tanto como gostava	❍ Só um pouco do que gostava	❍ Quase nada como gostava
Tenho uma sensação de medo, como se algo terrível estivesse para acontecer:	❍ Sinto, e muito forte	❍ Sim, mas não muito forte	❍ Um pouco, mas isso não me preocupa	❍ Não, de maneira nenhuma
Consigo rir-me e ver o lado divertido das coisas	❍ Tanto como costumava conseguir	❍ Agora, não tanto como costumava conseguir	❍ Definitivamente, não tanto como costumava conseguir	❍ Não, de maneira nenhuma
Tenho preocupações que me passam pela cabeça:	❍ A maior parte do tempo	❍ Muitas vezes	❍ De vez em quando, mas não muitas vezes	❍ Apenas ocasionalmente
Sinto-me alegre:	❍ Nunca	❍ Poucas vezes	❍ Às vezes	❍ A maior parte do tempo
Posso sentar-me à vontade e sentir-me relaxado:	❍ Sim, definitivamente	❍ Geralmente	❍ Poucas vezes	❍ Nunca
Sinto-me mais lento ou vagaroso:	❍ Quase sempre	❍ Muitas vezes	❍ Às vezes	❍ Nunca

Sinto uma espécie de medo, como se tivesse um aperto no estômago:	❍ Nunca	❍ Ocasionalmente	❍ Bastantes vezes	❍ Muitas vezes
Perdi o interesse pela minha aparência:	❍ Sim, definitivamente	❍ Não me cuido tanto como deveria	❍ Talvez não me cuide tanto como antes	❍ Cuido-me tanto como costumava
Sinto-me inquieto(a), como se tivesse que estar sempre a andar de um lado para o outro:	❍ Sim, muito	❍ Sim, bastante	❍ Não muito	❍ Não, de modo nenhum
Antecipo as coisas com satisfação:	❍ Tanto como eu costumava fazer anteriormente	❍ Um pouco menos do que anteriormente	❍ Muito menos do que anteriormente	❍ Quase nunca
Tenho sentimentos súbitos de pânico:	❍ Com muita frequência	❍ Bastantes vezes	❍ Não muitas vezes	❍ Nunca
Consigo apreciar um bom livro, um programa de televisão ou de rádio:	❍ Frequentemente	❍ Às vezes	❍ Poucas vezes	❍ Muito raramente

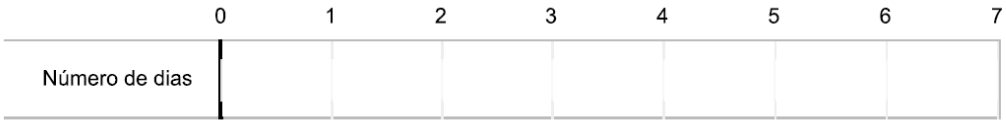
Questionário Impacto Fibromialgia

Burckhardt et al. (1991); Versão Portuguesa Rosado et al. (2006)

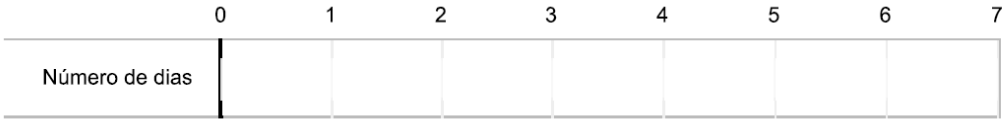
Instruções: Nas perguntas de 1 a 11 indique as opções que na última semana melhor descrevem a maneira como, em geral, foi capaz de executar as tarefas indicadas. Se habitualmente não faz uma dessas tarefas não responda a essa pergunta. Foi capaz de:

	Sempre	Quase sempre	Quase nunca	Nunca
1. Ir às compras?	❍	❍	❍	❍
2. Tratar da roupa na máquina de lavar/secar?	❍	❍	❍	❍
3. Cozinhar?	❍	❍	❍	❍
4. Lavar louça à mão?	❍	❍	❍	❍
5. Aspirar a casa?	❍	❍	❍	❍
6. Fazer as camas?	❍	❍	❍	❍
7. Andar vários quarteirões (200 a 500 metros)	❍	❍	❍	❍
8. Visitar a família ou os amigos?	❍	❍	❍	❍
9. Tratar das plantas ou praticar o seu passatempo?	❍	❍	❍	❍
10. Se deslocar, no seu próprio carro ou em transportes públicos?	❍	❍	❍	❍
11. Subir as escadas?	❍	❍	❍	❍

12. Na última semana, em quantos dias se sentiu bem?



13. Na última semana, quantos dias faltou ao trabalho e/ou não realizou as tarefas domésticas, devido à Fibromialgia?



Instruções: Nas perguntas que se seguem, assinale um ponto na linha que melhor indica o modo como, em geral, se sentiu na última semana:

14. Nos dias que trabalhou, quanto é que a sua doença – Fibromialgia – interferiu no seu trabalho?

Trabalhei sem problemas ——— Tive grande dificuldade no trabalho

15. Que intensidade teve a sua dor?

Não tive dor ——— Tive dor muito intensa

16. Que cansaço sentiu?

Não senti cansaço ——— Senti um cansaço enorme

17. Como se sentiu quando se levantava de manhã?

Acordei bem repousada									Acordei muito cansada

18. Que rigidez sentiu?

Não tive rigidez									Senti muita rigidez

19. Sentiu-se nervosa ou ansiosa?

Não tive ansiedade									Senti-me muito ansiosa

20. Sentiu-se triste ou deprimida?

Não me senti deprimida									Senti-me muito deprimida

HAQ

Fries et al. (1980); Versão Portuguesa Santos et al. (1996)

Estamos interessados em saber como é que a sua doença o afecta no seu dia a dia. Para cada questão numerada asinale uma e so uma resposta, aquela que que no seu entender melhor descreva as suas capacidades médias na SEMANA QUE PASSOU.

1. Vestir-se e arranjar-se. Consegue:

	Sem qualquer dificuldade	Com alguma dificuldade	Com muita dificuldade	Incapaz
Vestir-se incluindo abotoar a roupa e atar os sapatos?	❍	❍	❍	❍
Lavar o cabelo?	❍	❍	❍	❍

2. Levantar-se. Consegue:

	Sem qualquer dificuldade	Com alguma dificuldade	Com muita dificuldade	Incapaz
Erguer-se de uma cadeira?	❍	❍	❍	❍
Deitar e levantar-se da cama?	❍	❍	❍	❍

3. Comer. Consegue:

	Sem qualquer dificuldade	Com alguma dificuldade	Com muita dificuldade	Incapaz
Cortar a carne?	❍	❍	❍	❍
Levar à boca um copo ou chávena cheios?	❍	❍	❍	❍
Abrir pela primeira vez um pacote de leite de cartão?	❍	❍	❍	❍

4. Caminhar. Consegue:

	Sem qualquer dificuldade	Com alguma dificuldade	Com muita dificuldade	Incapaz
Caminhar fora de casa em terreno plano?	❍	❍	❍	❍
Subir cinco degraus?	❍	❍	❍	❍

5. Higiene. Consegue:

	Sem qualquer dificuldade	Com alguma dificuldade	Com muita dificuldade	Incapaz
Lavar e limpar todo o corpo?	❍	❍	❍	❍
Tomar banho?	❍	❍	❍	❍
Sentar e levantar-se da sanita?	❍	❍	❍	❍

6. Alcançar. Consegue:

	Sem qualquer dificuldade	Com alguma dificuldade	Com muita dificuldade	Incapaz
Alcançar e trazer até si um objecto de cerca de 2,5 kg colocado acima da sua cabeça?	❍	❍	❍	❍
Curvar-se e apanhar roupas caídas no chão?	❍	❍	❍	❍

7. Preensão. Consegue:

	Sem qualquer dificuldade	Com alguma dificuldade	Com muita dificuldade	Incapaz
Abrir as portas do carro?	❍	❍	❍	❍
Abrir as tampas de frascos que já tenham sido abertos?	❍	❍	❍	❍
Abrir e fechar torneiras?	❍	❍	❍	❍

8. Actividades. Consegue:

	Sem qualquer dificuldade	Com alguma dificuldade	Com muita dificuldade	Incapaz
Fazer compras e recados?	❍	❍	❍	❍
Entrar e sair de um carro?	❍	❍	❍	❍
Fazer a lida da casa (por ex. aspirar o pó, varrer ou fazer jardinagem)?	❍	❍	❍	❍

Assinale qual destes UTENSÍLIOS usa habitualmente:

- ❍ Bengala
- ❍ Andarilho
- ❍ Muleta ou canadiana
- ❍ Cadeira de rodas
- ❍ Auxiliares para se vestir (calçadeira comprida, fecho eclair especial, enfiador de botões, etc.)
- ❍ Adaptações na casa ou nos seus utensílios
- ❍ Cadeiras especiais
- ❍ Outro (descrever) _____

Assinale as actividades para cujo desempenho necessita habitualmente de OUTRA PESSOA:

- ❍ Vestir-se e arranjar-se
- ❍ Levantar-se
- ❍ Comer
- ❍ Caminhar

Assinale qual destes UTENSÍLIOS usa habitualmente:

- ❍ Sanita mais alta
- ❍ Banco para tomar banho
- ❍ Abre boiões (para boiões que tenham sido já abertos)
- ❍ Pegas na banheira
- ❍ Pinças de preensão
- ❍ Adaptações com pregas longas para a higiene pessoal
- ❍ Outro (descrever) _____

Assinale as actividades para cujo desempenho necessita habitualmente de OUTRA PESSOA:

- ❍ Higiene pessoal
- ❍ Alcançar objectos
- ❍ Agarrar e abrir objectos
- ❍ Lida doméstica e compras

AVALIAÇÃO DE DOR PELO DOENTE

Sem dor _____ Pior dor possível

SOCIAL DISTRESS SCALE

(Williams, 2000)

Para cada questão, indique o número que melhor representa os sentimentos que experienciou durante o jogo.

	1- Nada	2	3	4	5 - Extremamente
Senti-me "desligado"	❍	❍	❍	❍	❍
Senti-me rejeitado	❍	❍	❍	❍	❍
Senti-me um estranho	❍	❍	❍	❍	❍
Senti que pertenci ao grupo	❍	❍	❍	❍	❍
Senti que os outros jogadores interagiram muito comigo	❍	❍	❍	❍	❍

Para cada questão, indique o número que melhor representa os sentimentos que experienciou durante o jogo.

	1 - Nada	2	3	4	5 - Extremamente
Senti-me bem comigo próprio	❍	❍	❍	❍	❍
A minha auto-estima era elevada	❍	❍	❍	❍	❍
Senti-me apreciado	❍	❍	❍	❍	❍
Senti-me inseguro	❍	❍	❍	❍	❍
Senti-me insatisfeito	❍	❍	❍	❍	❍

Para cada questão, indique o número que melhor representa os sentimentos que experienciou durante o jogo.

	1 - Nada	2	3	4	5 - Extremamente
Senti-me invisível	❍	❍	❍	❍	❍
Senti-me sem sentido	❍	❍	❍	❍	❍
Senti-me como se não existisse	❍	❍	❍	❍	❍
Senti-me importante	❍	❍	❍	❍	❍
Senti-me útil	❍	❍	❍	❍	❍

Para cada questão, indique o número que melhor representa os sentimentos que experienciou durante o jogo.

	1 - Nada	2	3	4	5 - Extremamente
Senti-me poderoso	❍	❍	❍	❍	❍
Senti que tinha controlo sobre o curso do jogo	❍	❍	❍	❍	❍
Senti que tinha capacidade para alterar significativamente os acontecimentos	❍	❍	❍	❍	❍
Senti que era incapaz de influenciar as acções dos outros	❍	❍	❍	❍	❍
Senti que os outros jogadores decidiam tudo	❍	❍	❍	❍	❍

Para cada questão, indique o número que melhor representa os sentimentos que experienciou durante o jogo.

	1 - Nada	2	3	4	5 - Extremamente
Bem-estar	❍	❍	❍	❍	❍
Mal	❍	❍	❍	❍	❍
Hostilidade	❍	❍	❍	❍	❍
Zanga	❍	❍	❍	❍	❍
Prazer	❍	❍	❍	❍	❍
Felicidade	❍	❍	❍	❍	❍
Tristeza	❍	❍	❍	❍	❍

Para as questões seguintes, indique o número que melhor representa os seus pensamentos durante o jogo.

	1 - Nada	2	3	4	5 - Extremamente
Fui ignorado	❍	❍	❍	❍	❍
Fui excluído	❍	❍	❍	❍	❍

Assumindo que a bola foi lançada para cada participante um número semelhante de vezes (33%), que percentagem de lançamentos considera que recebeu? (indique um número entre 0 e 100)

_____

2. PUBLICATIONS RELATED TO THE CURRENT THESIS

Canaipa, R., Treister, R., Lang, M., Moreira, J., & Castro-Caldas, A. (2016). Feeling hurt: pain sensitivity is correlated with and modulated by social distress. *Clinical Journal of Pain,* 32(1), 14-19.

This publication was presented in Chapter 5. Rita Canaipa participated in the study design, data collection/processing, analysis and interpretation of the data, and writing of the manuscript.

Canaipa, R., Castro-Caldas, A., Moreira, J.M., Pimentel-Santos, F., Branco, J.C., Treister, R. Impaired pain modulation in Fibromyalgia patients in response to social distress manipulation. [Submitted to *Clinical Journal of Pain*]

This publication was presented in Chapter 6. Rita Canaipa participated in the study design, data collection/processing, analysis and interpretation of the data, and writing of the manuscript.

Feeling Hurt

Pain Sensitivity is Correlated With and Modulated by Social Distress

Rita Canaipa, MS,† Roi Treister, PhD,‡ Magdalena Lang, MD,‡ João M. Moreira, PhD,§ and Alexandre Castro- Caldas, MD, PhD†*

Objectives: Social distress, resulting from loss or threat to social relationships, shares similar psychological and neuronal processes with physical pain. Recent evidence demonstrated that social distress may have an impact on pain. The current study aimed to further assess the relationship between these 2 phenomena.

Materials and Methods: Sixty healthy participants were randomly assigned to inclusion, noninclusion, or exclusion conditions of Cyberball, a virtual ball tossing game used to induce social distress. Pain and unpleasantness in response to noxious electrical stimuli were assessed before and after Cyberball manipulation. Psychological characteristics were evaluated by the Experiences in Close Relationships Questionnaire and the neuroticism scale of Big Five Inventory.

Results: Significant correlations were found between social distress and pre-Cyberball unpleasantness thresholds: those who perceived the Cyberball task as more distressing demonstrated lower unpleasantness thresholds. Post-Cyberball manipulation pain intensity ratings, but not unpleasantness ratings, were lower in the inclusion condition. No associations were found between the psychological characteristic and the effects of Cyberball on pain or unpleasantness ratings.

Discussion: The current study results indicate that participants' pre-Cyberball unpleasantness threshold is related to their responsiveness to social distress and that physical pain may be modulated by social events. Further studies are needed to clarify the clinical relevance of these results.

Key Words: pain, social distress, social rejection, Cyberball

(*Clin J Pain* 2016;32:14–19)

The role of pain in organisms' survival is well known, yet human survival, as in many other species, also depends on social relations.[1] As such, the risk of losing social relationships can be as serious as actual physical threats.[2,3] As social attachment theory proposes,[4] social rejection events, involving threats to social bonds, may be particularly significant to mental[5] and physical health.[6] Accordingly, the term "social pain" is defined as pain resulting from loss, threat, or damage to social relationships.[7]

Social distress can be effectively induced in a laboratory setting with a variety of available techniques. For example, in the "Trier Social Stress Test," participants complete arithmetic tasks and deliver a free speech in front of a rejecting audience.[8] In the future life exclusion paradigm, participants complete a personality test and receive false feedback from the experimenter: they are informed that based on test results, it is expected that they will end up lonely in life.[9,10] Other studies have used real-life personal bereavement situations, in which strong affective reactions are induced by exposing participants to pictures of a lost loved one (a deceased or an ex-partner).[11–14]

"Cyberball" is another frequently used method,[15] in which participants believe they are playing a computerized virtual ball tossing game with other real participants. Social distress is induced, depending on the extent of participant inclusion by the "other players" in the game. Social distress is measured by the William's social distress questionnaire that assesses the impact of playing the game on 4 domains of psychological needs: belonging, self-esteem, meaningful existence, and control. In addition to these subscales, a total social distress score is calculated. Using the Cyberball paradigm, Eisenberger et al[16] elegantly demonstrated the bidirectional interactions of pain and social distress. In their study, the unpleasantness of pain stimuli was assessed at baseline and during the Cyberball paradigm. They demonstrated that those who perceived the stimuli as more unpleasant at baseline (ie, demonstrated lower pain unpleasantness thresholds) felt more distressed during the rejection episodes. In contrast, pain unpleasantness was affected by social distress: participants who felt more distressed during the rejection episodes also perceived higher unpleasantness in response to painful stimuli during the Cyberball manipulation. However, other studies have demonstrated an opposite relation between social distress and pain: DeWall and Baumeister[9] found increases in pressure pain thresholds and pain tolerance following social distress induced by the future life exclusion paradigm.

In sum, the present study aimed to further assess the relations between participants' sensitivity to physical pain and their susceptibility to social distress. We hypothesized that: (1) individuals who are more sensitive to physical pain would also be more sensitive to social exclusion situations; and that (2) induction of social distress would affect participants' pain ratings. Previous studies have shown the role

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of attachments style in rejection manipulations[17] and susceptibility to social distress,[18,19] thus, we assessed if attachment style affects relation between social distress and physical pain.

MATERIALS AND METHODS

Participants

Sixty participants were recruited from the undergraduate degree program of the Faculty of Psychology at the University of Lisbon. Participants received course credits for their participation.

Tools

Experimental Apparatus

Pain was induced by a bipolar felt pad electrode (Digitimer, Hertfordshire, England) placed on the left arm, near the wrist (posterior). The electrode, filled with conductive gel, was connected via extension cable to a constant current stimulator (model DS7A; Digitimer) in the experimenter room. The stimulator had a Bayonet Neill-Concelman connector trigger input socket that allowed the connection of a synchronizer (Plux Wireless Biosignals, SA, Lisbon, Portugal). The experimenter's computer "triggered" the stimulus in the form of a transistor-transistor logic trigger pulse, allowing the DS7A to be triggered externally.

Social Distress Manipulation

The Cyberball procedure was used to induce social distress as demonstrated by Eisenberger et al.[7] Cyberball is a virtual ball tossing game developed by Williams et al[15] to manipulate feelings of social rejection. In this procedure, participants believe that they are playing with other participants sitting at other computers elsewhere and connected via an internet network. In fact, however, the other 2 players are simulated by the software. The Cyberball manipulation comprises 3 study conditions: (1) in the inclusion condition, participants play with the other "players" and no social distress occurs. There are 2 exclusion conditions: (2) in the overtly excluded condition, at first the other "players" throw the ball to the participant, but then they start tossing the ball only between the 2 of them and the participant never again receives the ball. (3) In the noninclusion condition the same situation occurs, but the participant is informed that the other participants are unable to pass the ball to him/her due to technical problems.

Pain Stimulation Pre-Cyberball

Familiarization Trial. Participants were initially exposed to three 0.2 ms stimuli in intensities of 40, 60, and 80 mA to familiarize them with the procedure and with the pain and unpleasantness ratings. The participant rated each stimuli by moving sliders controlled by the mouse in 2 computerized visual analogue scales: pain intensity and pain unpleasantness. The scales aimed to assess sensory and emotional components of pain (respectively). On the first slider, they rated the perceived pain, ranging from 0, corresponding to "not painful at all" to 10, corresponding to "the worst pain one can imagine." On the second slider, they rated unpleasantness, ranging from 0, "not unpleasant at all" to 10, "the most unpleasant one can imagine."

Calibration. An ascending sequence, started with an intensity of 40 mA and augmented in 20 mA steps, was administered to individually adjust stimulation intensity. Stimuli duration was 0.2 ms with interstimuli intervals randomly distributed between 15 and 20 seconds. Participants rated stimuli intensities and unpleasantness ratings following each stimulus. The sequence was terminated when participants rated their pain as 6. The lowest stimulus intensity that was rated as painful was considered as the pain (or unpleasantness) threshold.

A second stimulation sequence was constructed based on the ascending sequence results. This was an 11-stimuli, random sequence calibrated so as to deliver equally spaced intensity stimuli between the threshold (intensity rated as 1) and the intensity rated as 6. These intensities were extrapolated for each participant to correspond a 0 to 10 scale with 11 stimulation intensities using the following formula—threshold stimulation intensity + 0.1 × (pain 6 stimulation intensity − threshold stimulation intensity) (this is an example for calculating intensity of 1, 0.2 instead of 0.1 was used to calculate "pain 2" intensity and so forth). Participant's responses to the second stimulation sequence were used for constructing the post-Cyberball stimulation sequence.

Pain Stimulation Post-Cyberball

At the end of the game, participants received 3 stimuli calibrated for targeting a pain intensity of 4. This was done by using a simple linear regression carried out for each participant individually immediately after the 11-stimuli sequence, yielding the required stimulus intensity for the next stage of the experimental procedure. The regression formula used was as follows: $(4-a)/b$ (a is the *mean* of the participants' intensities ratings in response to the 11 stimuli minus b multiplied by the mean of the intensities, b is the mean of the $\Delta x\Delta y$ divided by Δx^2). These 3 stimuli had the same duration and interval as in the previous sequence. In response to each stimulus, participants rated pain intensity and unpleasantness by using the computerized visual analogue scale. Post-Cyberball stimulation pain and unpleasantness were calculated as the mean response to these 3 stimuli.

Questionnaires

In addition to participant demographic information, the Experiences in Close Relationships questionnaire (ECR) were completed before Cyberball. After the Cyberball task, participants completed the social distress assessment and the neuroticism scale of the Portuguese version of the Big Five Inventory (BFI). These are described below in the order performed in the study.

ECR. Close relationship style was assessed by using the ECR,[20] which measures the 2 fundamental dimensions in adult attachment style: preoccupation and avoidance. It contains 36 items, rated on a 7-point scale, ranging from 1 "strongly disagree" to 7 "strongly agree," and a central point of 4 "neutral/mix." The Portuguese version of this questionnaire was developed by Moreira et al[21] and has been shown to have adequate psychometric properties.

Social Distress Assessment. As traditionally done in previous studies, the psychological impact of the Cyberball was assessed according to Williams et al,[15] with belonging (eg, "I felt disconnected"), self-esteem (eg, "I felt liked"), meaningful existence (eg, "I felt meaningless"), control (eg, "I felt I had control over the course of the game") subscales, with each item answered on a 5-point scale ranging from "not at all" to "extremely." The total score is obtained from

the average of subscales scores. This measure was used according to previous studies[7,16]: higher ratings indicate that the participants felt their psychological needs threatened to a greater degree and, as such, felt more socially distressed after the game. At the end of the study, participants were directly asked if they believed that they were playing with players from other laboratories.

Neuroticism Scale of the BFI. Participants completed the neuroticism scale of the Portuguese version of the BFI[22] to confirm that the impact of the Cyberball manipulation was not confounded by an individual tendency to appraise situations as threatening. This scale consisted of 7 items rated on a 5-point scale ranging from 1 for "strongly disagree" to 5 for "strongly agree." The Portuguese version was developed and validated by Moreira.[23]

Procedure

The study was approved by the Ethics and Deontology Commission of the Faculty of Psychology of University of Lisbon. As a first step of the study, on the morning of the experiment, participants completed online the demographic and Pre-Cyberball questionnaire (ECR) sent via e-mail. Later on the same day, participants came to the laboratory for the second part of the study. Informed consent was obtained from all participants before the beginning of each part of the study. Participants were told that the study aim was to assess the impact of working with video screens on the perception of pain. The participants were seated in a small room in front of a computer screen with the electrode attached to their wrist. This room was contiguous to the experimenter room but was separated by 2 doors so the experimenter could not see or interact with participants.

Following the pre-Cyberball pain calibration, each participant was randomly assigned to one of the 3 Cyberball conditions. Assignment was automatically done by the computer so that the experimenter did not know to which study condition participants were assigned to until the beginning of the Cyberball game. In the noninclusion condition, the experimenter entered the participants' room to inform about "technical problems" and ask the participant to continue concentrating on the game. At the end of the game, post-Cyberball pain stimulation was administered and questionnaires (social distress assessment and neuroticism scale of BFI) were completed. After completion of the entire procedure, participants were fully informed about the actual aims of the study and the rejection manipulation.

Statistical Analysis

Analyses were conducted by the SPSS for Windows, version 19 statistical package (SPSS Inc., Chicago, IL).[24] χ^2 and analysis of variance (ANOVA) tests were used to assess differences in demographic characteristics between study groups. ANOVA was utilized to assess differences between study conditions in pre-Cyberball pain and unpleasantness thresholds, psychological characteristics, social distress. Pearson correlation was used to study relations between pre-Cyberball pain and unpleasantness thresholds' social distress and psychological characteristics. The 1-sample t test was used to assess differences between post-Cyberball pain intensity and unpleasantness ratings and the predicted value of 4. Values are presented as means and SD. Results of all analyses were considered significant at the $P < 0.05$ level.

RESULTS

Participants' Characteristics and Manipulation Check

Of the 60 participants recruited to the study, 21 were assigned to the exclusion condition, 20 to the noninclusion, and 19 to the inclusion condition. In response to the question "did you believe that you were playing online with real participants," 9 participants answered negatively, and were excluded from further analyses. These 9 participants were from the inclusion condition (n = 2), the noninclusion condition (n = 1), and the exclusion condition (n = 6). Therefore, the final cohort consisted of 51 participants (n = 15 in the exclusion condition; n = 19 in the noninclusion; n = 17 in the inclusion), 43 females and 8 males with mean age of 20.6 years (SD = 3.5 y). Participants' sex (χ^2, $P = 0.093$), age (ANOVA, $P = 0.211$), and socioeconomic status (ANOVA, $P = 0.505$) did not significantly differ among Cyberball conditions.

Pre-Cyberball Pain and Unpleasantness Thresholds

Mean (± SD) intensities needed to induce pre-Cyberball pain and unpleasantness thresholds were 96.7 ± 64.4 mA (range between 20 and 320 mA) and 77.6 ± 47.5 mA (20 to 220 mA), respectively. ANOVA test revealed no significant differences in pre-Cyberball pain and unpleasantness thresholds between Cyberball conditions.

Social Distress

Mean (± SD) Social Distress scores after the Cyberball game were 3.35 ± 0.7 (minimum = 1.9, maximum = 4.6). One-way ANOVA revealed significant differences in social distress after the Cyberball game among Cyberball conditions ($F = 14.3$, $P < 0.001$). Specifically, Social Distress scores were significantly higher in the excluded condition (mean ± SD, 3.9 ± 0.49) than in the nonincluded (3.4 ± 0.49; $P = 0.016$) and the included condition (2.8 ± 0.62; $P < 0.001$). Social distress mean scores in the nonincluded condition were significantly higher than in the included condition ($P = 0.003$; Fig. 1). Descriptive statistics of the 2 attachment style subscales (avoidance and preoccupation) and the neuroticism total score are described in Table 1. ANOVA test revealed no significant differences among Cyberball conditions in any of these measures.

Relations Between Pre-Cyberball Pain and Unpleasantness Thresholds, and Social Distress

Our first hypothesis was partially confirmed, as demonstrated by the significant positive correlation between social distress and pre-Cyberball unpleasantness thresholds ($r = -0.358$, $P = 0.012$) but not with pre-Cyberball pain intensity thresholds ($r = 0.226$, $P = 0.119$). Psychological characteristics were not significantly correlated with pre-Cyberball pain or unpleasantness thresholds or with social distress.

Post-Cyberball Pain and Unpleasantness Ratings

Mean (± SD) of the perceived intensities of the post-Cyberball pain and unpleasantness ratings were 3.51 ± 1.1 and 3.95 ± 1.6, respectively. According to our second hypothesis, post-Cyberball pain intensity rating in the included condition (3.1 ± 0.8) was significantly lower than 4 (1-sample t test, $P = 0.001$), whereas post-Cyberball unpleasantness rating (3.9 ± 0.3) did not significantly differ

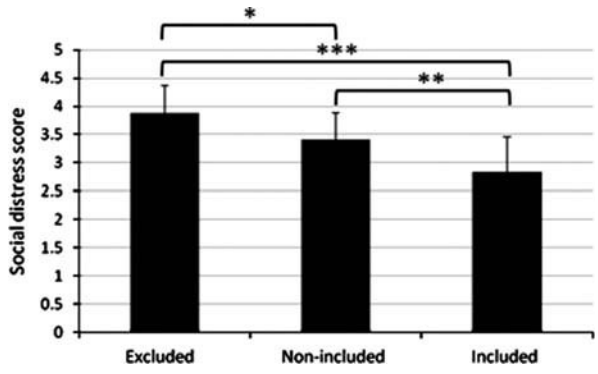

FIGURE 1. Social distress after Cyberball in the 3 game conditions. *$P<0.05$; **$P<0.01$; ***$P<0.001$.

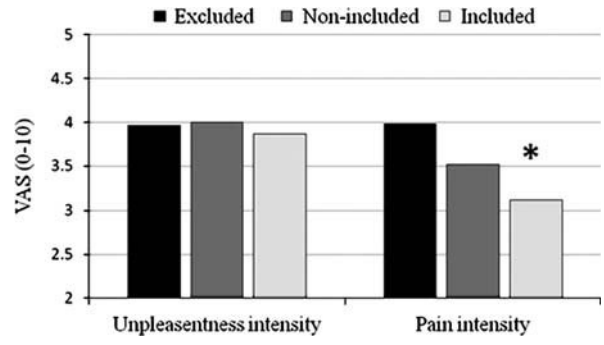

FIGURE 2. Pain and unpleasantness intensity after Cyberball in the 3 game conditions. *$P=0.001$, 1-sample t test, test value = 4. VAS indicates visual analogue scale.

from 4 ($P = 0.677$, Fig. 2). In the noninclusion condition, post-Cyberball pain (3.5 ± 1.3) and unpleasantness (4 ± 1.7) ratings were not significantly different from 4 ($P = 0.188$ and $P = 1$, respectively), as well as in the excluded condition (pain 4 ± 1.1; unpleasantness 4 ± 1.7).

DISCUSSION

The current study was aimed to shed more light on the complex relations between social distress and pain sensitivity. Our hypotheses were that (1) individuals who are more sensitive to physical pain would be more sensitive to social exclusion situations; and (2) induction of social distress would affect participants pain ratings. Both hypotheses were partly confirmed: The intensity needed to reach pre-Cyberball unpleasantness thresholds correlated with social distress. Following induction of social distress, patients in the inclusion condition (low social distress) perceived the painful stimuli as less painful than predicted.

Our first key finding was that social distress after Cyberball correlated with pre-Cyberball unpleasantness thresholds, but not with pre-Cyberball pain thresholds. Similarly, Eisenberger et al[16] used thermal stimuli and found correlations between social distress induced by Cyberball and baseline unpleasantness thresholds. However, Eisenberger et al[16] did not measure pain intensity. These relations between social distress and pain unpleasantness line up with imaging studies which demonstrated that social distress is linked to brain areas in which pain's emotional-cognitive dimensions are processed.[7,25] In any case, recent studies demonstrated mixed results[26,27] and therefore the extent to which pain and social distress share neurocognitive processes is yet to be determined.

Our second finding highlights the effect of social distress on pain. Specifically, following Cyberball, and in response to noxious electrical stimulation, participants who reported lower social distress (inclusion condition) perceived the stimuli as less painful, but not less unpleasant. In contrast, Eisenberger et al[16] have shown that during the social rejection conditions, social distress was positively correlated with unpleasantness ratings. These differences may be the result of differences between studies methodologies. First, in Eisenberger et al,[16] unpleasantness assessment was based on a 21-point scale, ranging from 0 "neutral" to 20 "unbearable" (with"10" representing the threshold) while pain intensity was not assessed at all. Second, painful stimuli in Eisenberger et al[16] were delivered during the Cyberball condition, whereas in the current study stimulation was performed after the social distress intervention. Third, time of social distress assessment also differed between studies, while Eisenberger et al[16] assessed social distress after participants were exposed to the painful stimulation, social distress in the current study was assessed immediately after Cyberball, before the painful stimulation. Finally, stimulus modalities also differed (electrical vs. thermal).

Interestingly, it has been shown that social distress induced by a different paradigm results in analgesia, rather than hyperalgesia: DeWall and Baumeister[9] demonstrated a "numbness reaction" following induction of social distress by using the future life exclusion paradigm. Specifically, increases in pressure pain thresholds and pain tolerance were observed following the manipulation. The authors suggested that anticipation of future rejection lead to a response of "numbness" in order to avoid greater suffering. A later study directly compared the impact of social distress induced by the Cyberball paradigm with the future life exclusion paradigm.[28] Although hyperalgesia (diminished threshold and tolerance to cold stimuli) was found in the excluded group following the Cyberball paradigm, an opposite effect of analgesia was induced by the future life exclusion paradigm. The authors interpreted these results in accordance to a severity hypothesis: Cyberball may be a less severe "social injury," leading to hypersensitivity, whereas future life exclusion might be more severe, leading to hyposensitivity.

Another possible explanation might be related to the complex interactions between stress and pain. As a known fact, stress may result in analgesia or hyperalgesia.[29,30] Evidence from animal studies have demonstrated that in case there is a lack of information to guide a response, as

TABLE 1. Participants' Scores in the Questionnaires

	Mean ± SD	Minimum	Maximum
ECR avoidance	70.6 ± 15.3	38	98
ECR preoccupation	12.6 ± 5.3	4	26
BFI neuroticism	21.8 ± 4.6	8	30

BFI indicates Big Five Inventory; ECR, Experiences in Close Relationships questionnaire.

may occur in the Cyberball game, arousal may induce hyperalgesia. Indeed, being excluded in Cyberball induces higher skin conductance level, a measure of arousal, compared with inclusion.[31]

Notably, our results suggest that social rejection does not increase pain ratings or unpleasantness but, rather, that social inclusion helps to reduce pain. One might argue that the observed effects are actually due to social support, rather than social distress. However, the fact that social distress was induced in all participants (there were no "0" scores in social distress scale), implies that this is probably not the case. Other explanations might be related to our specific methodology (ie, our painful stimuli protocol). This issue deserves further investigation.

No relations between social distress and any of the studied psychological measures were found in the current study. In contrast, MacDonald[17] studied the effect of social distress induced by 2 paradigms, Cyberball and recalling past exclusion experiences, on pain. They concluded that participants attachment styles might have an important role in the effects of social distress on pain. Similar to Eisenberger et al's[16] results, we found no relations between neuroticism and social distress or pain in our study. This may suggest that stress induced by Cyberball is specific and cannot be explained by a general tendency to appraise events as threatening. In contrast, Riva et al[32] have recently demonstrated that fear of social threat modulates sensitivity to social distress. Future studies are warranted to assess the effects of psychological characteristics on social distress and pain.

Several limitations of the current study deserve considerations: (1) during threshold assessment, some participants rated "2" (on the 0 to 10 scale) in response to the first stimulus that was perceived as painful (threshold). This implies that we should have used smaller increases in stimulus intensities between consecutive stimuli during threshold assessments. (2) The number of participants excluded because their disbelief in the Cyberball game differed among conditions, something that may have undermined random assignment. (3) Our pain stimulation protocol implied different pain intensities premanipulation and postmanipulation. This limits our ability to easily understand manipulation effects. Finally, our relatively small sample size may have led to low power and to the inability to detect significant effects.

The current study, together with previous studies, indicates that sensitivity to pain relate to sensitivity to social distress. The effects of social distress on pain are particularly relevant in those chronic pain conditions that are known to be "stress related." A better understanding of the impact of social events on chronic pain patients can help health care providers and patients to better diagnose and deal with the painful conditions. Future studies aimed at throwing light onto mechanisms underlying these relationships will hopefully help in the development of new treatment approaches.

REFERENCES

1. Panksepp J. *Affective Neuroscience: The Foundations of Human and Animal Emotions*. Oxford: University Press; 1998.
2. Eisenberger NI, Lieberman MD. Why rejection hurts: a common neural alarm system for physical and social pain. *Trends Cogn Sci*. 2004;8:294–300.
3. Macdonald G, Leary MR. Why does social exclusion hurt? The relationship between social and physical pain. *Psychol Bull*. 2005;131:202–223.
4. Bowlby J. *Attachment and Loss*.2: New York: Basic Books; 1973.
5. Monroe SM, Rohde P, Seeley JR, et al. Life events and depression in adolescence: relationship loss as a prospective risk factor for first onset of major depressive disorder. *J Abnorm Psychol*. 1999;108:606–614.
6. Mikulincer M, Florian V. The relationship between adult attachment styles and emotional and cognitive reactions to stressful events. In: Simpson J, Rholes S, eds. *Attachment Theory and Close Relationships*. New York: Guilford Press; 1998:143–165.
7. Eisenberger NI, Lieberman MD, Williams KD. Does rejection hurt? An fMRI study of social exclusion. *Science*. 2003;302:290–292.
8. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'—a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*. 1993; 28:76–81.
9. DeWall CN, Baumeister RF. Alone but feeling no pain: effects of social exclusion on physical pain tolerance and pain threshold, affective forecasting, and interpersonal empathy. *J Pers Soc Psychol*. 2006;91:1–15.
10. Twenge JM, Baumeister RF, Tice DM, et al. If you can't join them, beat them: effects of social exclusion on aggressive behavior. *J Pers Soc Psychol*. 2001;81:1058–1069.
11. Gündel H, O'Connor MF, Littrell L, et al. Functional neuroanatomy of grief: an FMRI study. *Am J Psychiatry*. 2003;160:1946–1953.
12. Kersting A, Ohrmann P, Pedersen A, et al. Neural activation underlying acute grief in women after the loss of an unborn child. *Am J Psychiatry*. 2009;166:1402–1410.
13. Kross E, Egner T, Ochsner K, et al. Neural dynamics of rejection sensitivity. *J Cogn Neurosci*. 2007;19:945–956.
14. Kross E, Berman MG, Mischel W, et al. Social rejection shares somatosensory representations with physical pain. *Proc Natl Acad Sci USA*. 2011;108:6270–6275.
15. Williams KD, Cheung CKT, Choi W. Cyberostracism: effects of being ignored over the internet. *J Pers Soc Psychol*. 2000;79:748–762.
16. Eisenberger NI, Jarcho JM, Lieberman MD, et al. An experimental study of shared sensitivity to physical pain and social rejection. *Pain*. 2006;126:132–138.
17. MacDonald G. Use of pain threshold reports to satisfy social needs. *Pain Res Manag*. 2008;13:309–319.
18. Karremans JC, Heslenfeld DJ, van Dillen LF, et al. Secure attachment partners attenuate neural responses to social exclusion: an fMRI investigation. *Int J Psychophysiol*. 2011;81:44–50.
19. DeWall CN, Masten CL, Powell C, et al. Do neural responses to rejection depend on attachment style? An fMRI study. *Soc Cogn Affect Neurosci*. 2012;7:184–192.
20. Brennan KA, Clark CL, Shaver PR. Self-report measurement of adult romantic attachment: an integrative overview. In: Simpson JA, Rholes WS, eds. *Attachment Theory and Close Relationships*. New York: Guilford Press; 1998:46–76.
21. Moreira JM, Lind W, Santos MJ, et al. Experiences in Close Relationships: a questionnaire assessing the basic dimensions of attachment styles in adults: Translation and validation for the Portuguese population. *Laboratório de Psicologia*. 2006;4:3–27.
22. John OP, Srivastava S. The Big Five trait taxonomy: history, measurement, and theoretical perspectives. In: Pervin LA, John OP, eds. *Handbook of Personality: Theory and Research*. New York: Guilford; 1999:102–138.
23. Moreira JM. Altera Pars Auditur: The Dual Influence of the Quality of Relationships Upon Positive and Negative Aspects of Coping With Stress. 2002; Unpublished doctoral dissertation; University of Lisbon, Portugal.
24. IBM Corp. *IBM SPSS Statistics for Windows, Version 190*. Armonk, NY: IBM Corp.; 2010.

25. Eisenberger NI. The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. *Nat Rev Neurosci*. 2012;13:421–434.
26. Cacioppo S, Frum C, Asp E, et al. A quantitative meta-analysis of functional imaging studies of social rejection. *Sci Rep*. 2013;3:20–27.
27. Woo CW, Koban L, Kross E, et al. Separate neural representations for physical pain and social rejection. *Nat Commun*. 2014;5380:1–12.
28. Bernstein MJ, Claypool HM. Social exclusion and pain sensitivity: why exclusion sometimes hurts and sometimes numbs. *Pers Soc Psychol Bull*. 2012;38:185–196.
29. Jørum E. Analgesia or hyperalgesia following stress correlates with emotional behavior in rats. *Pain*. 1988;32: 341–348.
30. Vidal C, Jacob J. Hyperalgesia induced by emotional stress in the rat: an experimental animal model of human anxiogenic hyperalgesia. *Ann N Y Acad Sci*. 1986;467:73–81.
31. Kelly M, McDonald S, Rushby J. All alone with sweaty palms—physiological arousal and ostracism. *Int J Psychophysiol*. 2012;83:309–314.
32. Riva P, Williams KD, Gallucci M. The relationship between fear of social and physical threat and its effect on social distress and physical pain perception. *Pain*. 2014;155:485–493.

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O processamento da dor física e da dor social

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Resumo

A experiência da dor encontra-se entre as mais intensas e marcantes experiências humanas. É parte integrante da dialéctica com o mundo exterior, estruturando os nossos limites fisiológicos e psicológicos permanentemente. Tem um valor fundamental na sobrevivência, garantindo o afastamento de estímulos e situações que poderiam ameaçar a vida. Conhecida por todos os ser humanos e, infelizmente, presente cronicamente em muitos deles, representa um desafio à compreensão científica. Nos últimos anos as Neurociências têm conseguido caracterizar os processos biológicos envolvidos na dor, bem como o papel que o contexto emocional, social e cultural pode ter nesta experiência.

De entre as várias emoções que podem modular o processamento da dor física, a dor social, isto é, a dor que ocorre em situações de perda de relações sociais significativas, partilha processos comportamentais, neurocognitivos e moleculares com a dor física (Eisenberger, 2012). Nesta perspectiva, um indivíduo que seja capaz de antecipar adequadamente os riscos para a sua integridade física, evitando situações em que possa sentir dor, mas não seja capaz de antecipar os perigos sociais, afastando-se ou sendo rejeitado pelo grupo, pode ficar igualmente em situação de risco do ponto de vista da sua sobrevivência. Diversos estudos têm procurado compreender de que forma estes dois fenómenos se poderão relacionar. São estes estudos que procuramos aqui rever, na expectativa de clarificar a pertinência desta área de investigação e o potencial clínico que o conhecimento das interligações entre estes tipos de dor poderá ter na prática clínica, sobretudo na dor crónica.

A experiência da dor física

Apesar das dificuldades em definir a dor, a *International Association for the Study of Pain* alcançou algum consenso científico ao caracterizá-la como uma "experiência sensorial e emocional desagradável associada ao dano actual ou potencial dos tecidos, ou descrita em termos desse dano". Nesta definição destaca-se a complexidade da dor, quer pela conjugação das dimensões sensoriais e emocionais quer pelo reconhecimento do seu carácter de experiência privada, que não se limita às situações de evidência de lesões físicas observáveis. De facto, em muitos processos de dor, não é clara, ou é mesmo inexistente, a evidência da causa ou localização da lesão.

Podemos compreender o processamento da dor de forma simplificada, imaginando o que ocorre aquando de uma picada de agulha, por exemplo. Essa picada vai activar os receptores de dor dos nervos que se encontram na zona lesionada, ou seja, os nociceptores. Uma vez activados esses receptores, geram-se potenciais de acção que seguem ao longo das fibras nociceptoras até atingir a espinhal medula, onde ocorre a libertação de neurotransmissores que vão, posteriormente, activar outras fibras que activarão, finalmente, várias áreas do tronco e córtex cerebral (Woolf & Salter, 2000). Em geral, podem destacar-se a existência de dois sistemas de processamento da dor: o sistema de dor lateral e o sistema de dor médio (Porro, 2003). O sistema de dor lateral é o responsável pelo componente sensorial-discriminativo da dor, processa informação sobre os aspectos sensoriais, permitindo detectar que parte do corpo dói, qual a intensidade da dor e que tipo de sensação é (se é semelhante a uma picada, queimadura, repelão, latejo, etc.). Para processar esses dados, a informação que atinge a espinhal medula, vai encaminhar-se para as áreas do cérebro que analisam informação sensorial, sobretudo, as áreas somatosensoriais e a parte posterior do córtex da ínsula.

O sistema de dor médio participa activando processos cognitivos e afectivos. É este sistema que garante a desagradabilidade da dor e o desencadear de vários processos atencionais e cognitivos na sua presença. Para este efeito este sistema recruta, sobretudo, áreas do córtex pré-frontal, o córtex do cíngulo anterior, e também a ínsula anterior. Outras regiões do cérebro, para além das laterais e médias descritas, podem também contribuir significativamente para a experiência da dor, dependendo de vários factores internos e externos, como o estado físico, o humor, as crenças e o contexto onde ocorre a dor, entre muitos outros factores (Tracey & Mantyh, 2007).

Qualquer tipo de dor, em qualquer pessoa e associada a qualquer situação de saúde tem sempre estes dois componentes. Na dor, não há sensação física sem emoção. Se a dor não fosse desagradável, por que razão se afastaria a agulha que pica? Certamente se permitiria que continuasse a picar e a destruir esses tecidos. Como a dor é desagradável, logo após a picada, manusear-se-á essa agulha com outro cuidado! A dimensão cognitivo-afectiva da dor é, por isso, fundamental para a preservação da integridade física. Algumas situações raras, analgesia congénita,

foram descritas em pessoas que são incapazes de processar a desagradabilidade da dor. O que poderia parecer à partida uma vantagem, não poder experienciar dor, acaba contudo por conduzir estas pessoas a uma morte precoce, fruto da incapacidade de antecipar e de afastar situações em que o organismo se encontra em risco. Contudo, há situações igualmente intrigantes, em que a pessoa parece sentir dor sem que se detecte qualquer lesão. Ainda que não seja fácil compreender o que justifica muitas das queixas de dor que enchem consultas médicas e exames complementares, tudo indica que o sistema neuronal que processa a dor nestas pessoas, funciona de uma forma diferente quando comparadas com pessoas saudáveis. As situações de dor crónica resultam de um processamento demasiado eficiente da dor, traduzindo-se numa maior activação dos diversos neuroquímicos e áreas neuronais que processam os estímulos dolorosos. Falar sobre a dor crónica está para além dos objectivos do presente artigo, mas as alterações neuronais daí decorrentes, bem como o papel que as emoções desempenham nesse processo revela-se extremamente interessante. (para uma revisão ver Tracey & Bushnell, 2009).

Modulação da dor física pelas emoções

Quando as queixas de dor são muito exacerbadas, é bastante frequente ouvirmos, de quem observa estes "queixosos" que as emoções são as "obreiras" por detrás dessa dor. Na verdade, quem não sentiu ainda uma forte dor de cabeça após um episódio de tensão emocional? Ou quem não viu essa mesma dor de cabeça desaparecer no momento em que a atenção se dispersa para tema mais feliz: o filme que queria ver e começou mesmo agora, o telefonema amigo que faz esquecer a sensação de dor?

De facto, as emoções modulam significativamente a experiência da dor, existindo uma forte ligação entre emoções negativas e aumento da dor e entre emoções positivas e diminuição da dor (Wiech & Tracey, 2009). De um ponto de vista neuronal, tem sido sugerido que esta modulação depende do chamado "sistema modulador descendente da dor" (Tracey & Mantyh, 2007). As emoções são processadas, como referimos, no córtex pré-frontal e nas áreas do cíngulo anterior, e essas áreas encontram-se em ligação com núcleos que se encontram no tronco cerebral (sobretudo a substância periaqueductal cinzenta e os núcleos ventromediais rostrais no bolbo raquidiano). Estes núcleos comunicam com a espinhal medula, através de vias descendentes, tendo assim capacidade de controlar o processamento da dor nos tecidos periféricos. Este sistema modulador descendente da dor tanto pode ter um efeito inibitório no processamento da dor, isto é, analgésico, como pode ter um efeito excitatório no processamento da dor, isto é hiperalgésico.

Naturalmente, muitos estudos se desenvolveram no sentido de compreender que emoções podem ser mais influentes e, de que forma e quanto, poderão elas alterar a experiência da dor.

Processamento da dor social

De entre estes diversos estímulos emocionais, tem sido proposto que os estados emocionais que se relacionam com as dimensões sociais poderão ter um papel ainda mais importante, do que as emoções negativas em geral, na modulação da dor física. A ideia central que fundamenta esta perspectiva é a de que, os mamíferos, por serem animais que se desenvolvem em grupos sociais, dependem não apenas da integridade física mas de uma boa integração social. Nestes animais, a ligação ao grupo social é essencial à sobrevivência, pois o grupo garante protecção, acasalamento, procura e partilha de recursos. Sobretudo nos humanos, o longo período de dependência em relação aos progenitores justifica a necessidade e importância de mecanismos biológicos no sentido da manutenção das ligações sociais. Bowlby (1973) estudou este sistema, a que chamou sistema de vinculação e mostrou a importância que uma relação segura entre cuidador e bebé, pode ter no bem-estar emocional na infância, mas também na vida adulta.

Nas últimas décadas, vários estudos têm corroborado esta ideia, mostrado que as situações que envolvem ruptura de relações sociais são muito significativas para a saúde mental (Monroe, Rohde, Seeley, & Lewinsohn, 1999) e física (Mikulincer & Florian, 1998). As situações de rejeição social são os acontecimentos de vida mais implicados na Depressão e têm uma capacidade três vezes superior de desencadear Depressão do que outros acontecimentos, que não se relacionam com a esfera social, como por exemplo, a perda de emprego (Kendler, Hettema, Butera, Gardner, & Prescott, 2003). Para além disso, estas situações estão ainda relacionadas com um aumento da reactividade do Eixo Hipotálamo-Hipofisário, que regula as respostas neuroendocrinas do stress (Dickerson & Kemeny, 2004). Tal como ocorre nas situações de dor física, um aumento de citoninas pró-inflamatórias (células relacionadas com resposta inflamatória) e um aumento das respostas de cortisol (hormona cuja produção aumenta em situação de stress) foi verificado em situações de rejeição social. Alguns estudos (por exemplo, Gruenewald, Kemeny, Aziz, & Fahey, 2004) evidenciaram também que uma tarefa passava a induzir uma resposta de cortisol mais elevada e com impacto durante mais tempo, se envolvesse também desvalorização e rejeição social. Assim, as situações de risco social, ao envolverem alterações em parâmetros do sistema neuroendocrino e ao promoverem a produção de citocinas pró-inflamatorias, predispõem os indivíduos que delas padecem à doença, promovendo do ponto de vista social um "comportamento de doente" que envolve apatia, humor depressivo e isolamento social (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Um evidente ciclo vicioso, que se reconhece no comportamento social de indivíduos com várias doenças, como as relacionadas com a dor crónica.

Baseados neste pressuposto da importância das relações sociais, Eisenberger, Lieberman e Williams (2003) propõem a existência da "dor social". Este conceito refere-se ao sofrimento que

decorre da perda ou ameaça na integridade das relações sociais significativas. Na perspectiva dos autores, as semelhanças entre estes tipos de dor encontram-se em expressões verbais frequentemente utilizadas, como "coração partido" ou "fiquei magoado", que remetem para dimensões físicas as experiências relacionadas com a esfera social (Macdonald & Leary, 2005), e encontram-se ainda em diversos mecanismos neurocognitivos.

Em 2003, este grupo de investigação mostrou pela primeira vez quais as áreas neuronais que se activavam quando um indivíduo se sente rejeitado socialmente. Para isso, os participantes jogaram um jogo virtual, o *Cyberball*, enquanto eram obtidas as imagens de ressonância magnética funcional. O *Cyberball* trata-se de um jogo criado por Williams (2000) para estudar rejeição social. É bastante simples, implicando apenas que participante passe a bola a outros dois jogadores, que ele pensa serem jogadores "reais", que estão noutros laboratórios a realizar a experiência. Na verdade, o participante está, sem saber, a jogar sozinho com o computador que determina se será ou não excluído, de acordo com os objectivos do investigador. Assim, este jogo permite a criação de três condições, a primeira, a situação de inclusão, em que o participante joga com os outros, sendo-lhe passada a bola um número semelhante de vezes. A segunda situação, é a chamada situação de exclusão, onde após uma fase inicial em que o participante joga, os outros dois jogadores deixam de lhe passar a bola e jogam apenas entre si. Por fim, na terceira condição, considerada de controlo e semelhante à situação de exclusão, o participante é informado que devido a um problema técnico não pode jogar, podendo apenas observar os outros jogadores. Ainda que a situação do jogo seja uma situação de exclusão num grupo que o participante não conhece e seja pouco pessoal, foi possível verificar nesse estudo e em muitos outros que lhe seguiram que o *Cyberball* tem poder suficiente para gerar sentimentos de rejeição social e alterar respostas psicofisiológicas, como o nível de condutância da pele (Kelly, McDonald, & Rushby, 2012).

Para além de verificarem que o jogo induz rejeição social, os autores verificaram ainda que estes sentimentos de rejeição social envolviam a activação do córtex do cíngulo anterior, nas áreas dorsais, e a ínsula anterior, as áreas que também processam a desagradabilidade da dor física. A componente cognitivo-afectiva da dor parece, deste modo, unir estes dois tipos de experiência.

Partindo destes dados, os autores defenderam a ideia de que para os animais que vivem integrados em grupos sociais deverá existir um "alarme neuronal" que sinalizará as situações de risco do ponto de vista físico e as situações de risco do ponto de vista social, por forma a que o indivíduo procure reencontrar o equilíbrio físico e psíquico (Eisenberger & Lieberman, 2004). Na proposta de semelhança entre "dor física" e "dor social", a função de alarme neuronal seria desempenhada pelo córtex do cíngulo anterior, na sua porção dorsal, que se activaria quer pelo sistema de vinculação social quer pelo sistema de dor física. Em defesa desta hipótese, têm sido ainda utilizados os dados de estudos com animais e com humanos que demonstram que os opiodes, para além de terem um

papel bem definido na dor, também poderão regular a dor emocional que resulta da ansiedade de separação nas relações próximas (Panksepp, 2005). Mais recentemente, Way, Taylor e Eisenberger (2009), foram mesmo capazes de mostrar que a sensibilidade à dor social se relaciona com os polimorfismos dos genes dos receptores dos opiodes. Nesta perspectiva, as semelhanças entre dor física e social são fortes e podem ser encontradas desde a sua base comportamental até à molecular.

Alguns autores foram mais longe na defesa dos paralelismos entre estes dois tipos de experiência de sofrimento e consideraram que seria possível identificar mais áreas neuronais comuns entre dor física e dor social, se a rejeição social invocada fosse mais intensa (Kross, Berman, Mischel, Smith, & Wager, 2011). Assim, ao invés de obterem as imagens de ressonância magnética funcional em indivíduos que eram rejeitados no *Cyberball*, obtiveram as imagens quando indivíduos recém-separados visualizavam fotografias dos parceiros que os haviam rejeitado. Nestas situações de rejeição mais pessoais e mais intensas, verificaram que ocorriam activações não apenas do córtex do cíngulo anterior e da ínsula anterior, que processam o componente cognitivo-afectivo da dor, mas também das áreas somatosensoriais secundárias e da ínsula posterior, que processam o componente sensorial-discriminativo.

Críticas às perspectivas que defendem as semelhanças entre dor física e dor social

Estas perspectivas têm angariado, também, bastantes críticas (Iannetti & Mouraux, 2011). Apesar de as situações de dor física e as situações de rejeição social, implicarem sofrimento e serem relevantes para o bem-estar, e sobrevivência, são experiências bastante diferentes. Activações do córtex do cíngulo anterior e da ínsula anterior ocorrem num vasto conjunto de situações emocionais que incluem a dança, a percepção do tempo, a consciência do ritmo cardíaco (Craig, 2009) e não apenas a dor física. Estas áreas activam-se em diversas tarefas sensoriais, desde que envolvam o processamento de estímulos cognitivos multimodais com alguma saliência atencional. Sabemos hoje que o processamento neuronal associado à dor, ou a qualquer outro processo cognitivo ou emocional, envolve sempre um amplo conjunto de áreas neuronais. Não é muito fácil, nem muito precisa a ideia de que poderá existir um conjunto de áreas tão específico para cada um, ou para ambos os tipos de dor.

Mais recentemente, uma revisão sistemática dos estudos de neuroimagem que envolvem "rejeição social", induzida experimentalmente através do *Cyberball* ou do reviver de episódios que envolvem separações de parceiros, foi ainda mais longe nas críticas. Este estudo mostrou, mesmo, que as áreas activadas nestas situações sociais poderão não ser sobreponíveis com as áreas activadas em situação de dor física (Cacioppo, Frum, Asp, Weiss, Lewis, & Cacioppo, 2013). Ainda que a dor física e dor social partilhem a dimensão do "sofrimento", a partilha portanto, da saliência

emocional, não são invocados pelos mesmos estímulos. A rejeição social, não é uma experiência sensorial nos mesmos termos que um estímulo físico é.

Apesar da pertinência destas críticas, consideramos que o facto de as áreas neuronais activadas não serem as mesmas em ambas as situações, como tudo indica que seja o caso, em nada altera a importância da interligação entre estas duas experiências.

Modulação da dor física pela dor social

Mais do que a discussão das activações cerebrais, parece-nos importante compreender o papel modulador que a dor social poderá ter na dor física. Um primeiro estudo (Eisenberger, Jarcho, Lieberman, & Naliboff, 2006) realizado nesse âmbito e que utilizou também o *Cyberball*, mostrou que os indivíduos que se sentiam mais rejeitados na situação de exclusão do jogo eram os que tinham um limiar para a dor física mais baixo. Para além disso, esse estudo mostrou ainda que os indivíduos que eram mais sensíveis à situação de exclusão sentiam os estímulos dolorosos que lhes eram aplicados durante o jogo, como mais desagradáveis. Este estudo baseou-se na ideia de que a relação entre dor social e dor física ocorre ao nível do componente cognitivo-afectivo. Por essa razão, os autores analisaram o impacto das diferentes condições do *Cyberball* apenas na percepção da "desagradabilidade" da dor, mas não analisaram a correlação com a intensidade da dor física.

Procurando clarificar esta questão realizámos recentemente um estudo (Canaipa, Treister, Moreira e Castro-Caldas, submetido) com o objectivo de compreender de que forma as diferentes condições do jogo podem relacionar-se com a percepção de dor, em termos da sua intensidade e desagradabilidade. Em primeiro lugar, verificámos tal como no estudo anterior, que os indivíduos que se sentiam mais rejeitados eram, de facto, aqueles que haviam apresentado, antes mesmo de iniciarem o jogo, um limiar para a desagradabilidade da dor mais baixo. Em segundo lugar, verificámos que as situações de rejeição social não aumentaram a percepção da intensidade da dor, mas as situações de inclusão diminuíam a percepção da intensidade da dor aos estímulos eléctricos, aplicados depois do jogo. Foi possível verificar portanto, a outra face da importância das dimensões sociais. Se a dor social pode estar relacionada com um aumento da percepção da dor, sobretudo em termos da sua desagradabilidade ou seja, pode induzir hiperalgesia, um bom funcionamento social parece ser analgésico.

Outros autores utilizaram diferentes tarefas experimentais, como um falso *feedback* a um suposto questionário de personalidade (DeWall & Baumeister, 2006). Nesta tarefa, os participantes são informados que, de acordo com as respostas que deram a esse questionário, é possível prever que terão muitos problemas de relacionamento no futuro e acabarão sozinhos. Estranhamente, esta situação diminuiu a percepção de dor, contrariando os estudos anteriores. Um trabalho posterior

comparou, finalmente, a utilização destas duas formas de indução de rejeição social (*Cyberball* e antecipação de futuro sozinho) e concluiu que o *Cyberball* poderá ser uma situação de menor "intensidade de rejeição social" e por isso tender a estar relacionado com um aumento da percepção da dor (Bernstein & Claypool, 2012). Pelo contrário, ser informado de que se acabará sozinho no futuro, poderá ser considerado uma situação de tal forma intensa que induzirá uma espécie de "estado de choque" que torna os indivíduos menos sensíveis aos estímulos que lhe são aplicados posteriormente, para evitar sofrimento no longo prazo.

Acreditamos, contudo, que outras explicações, bastante mais interessantes do ponto de vista neuronal, são possíveis para estas diferenças, nomeadamente as que decorrem das relações entre *stress* e dor. Os estudos com modelos animais têm mostrado que as situações de *stress*, tanto podem conduzir a analgesia como a hiperalgesia (Jørum, 1988; Vidal & Jacob 1986). Quando existe informação para guiar o comportamento e alguma capacidade de antecipação sobre o que se seguirá, tende a ocorrer analgesia; mas se não existir informação e o desfecho da situação for imprevisível, tende a ocorrer hiperalgesia. Existe um amplo conjunto de outras variáveis individuais, como o género e até o contexto social e cultural, que participam também como mediadoras do impacto do *stress* na dor (por exemplo, Racine Tousignant-Laflamme, Kloda, Dion, Dupuis, & Choinière, 2012). Compreender estes efeitos moduladores exige mais investigação e, desenhos experimentais criativos e parcimoniosos.

Em resumo

O estudo dos processos de modulação da dor tem sido intenso nos últimos anos e abrange, como referimos ao longo desta revisão, não apenas os mecanismos comportamentais, neurocognitivos, mas também, cada vez mais os mediadores neuromoleculares. Nesse sentido, clarificar de que forma a dor social poderá modular a dor física em indivíduos saudáveis, poderá constituir um primeiro passo para compreender a relevância dos processos sociais na etiologia e no desenvolvimento de situações de dor crónica, particularmente naquelas que parecem estar mais relacionadas com o *stress*.

Estudar a dor social parecem-nos importante também quando constatamos que as alterações estruturais (como a diminuição de volume de substância cinzenta), neuroquímicas (como alterações ao nível das concentrações de glutamato e de opioides) e funcionais (aumento das activações em áreas neuronais relacionadas com as emoções) que se identificam na dor crónica, ocorrem em áreas neuronais que estão relacionadas com processos sociais e emocionais, ou são moduladas por estes (Tracey & Mantyh, 2007). Apesar de perturbações psicológicas, como a Depressão e Ansiedade, serem concomitantes à dor crónica ainda hoje é difícil compreender de que forma os processos

físicos e emocionais se inter-relacionam e, participam na sua etiologia e desenvolvimento. Clarificar estas relações poderá ser fundamental para futuras abordagens terapêuticas e, para alívio do sofrimento psicológico e físico destes doentes. Por todas estas razões, esperamos ter sido capazes de mostrar o estado da arte da investigação nesta área e justificar porque consideramos esta jornada científica da maior relevância.

Referências

Bernstein, M.J., & Claypool, H.M. (2012). Social exclusion and pain sensitivity: why exclusion sometimes hurts and sometimes numbs. *Pers Soc Psychol Bull, 38*, 185-96.

Bowlby, J. (1973). *Attachment and loss* (Vol. 2). New York: Basic Books.

Cacioppo, S., Frum, C., Asp, E., Weiss, R.M., Lewis, J.W., & Cacioppo JT. (2013). A quantitative meta-analysis of functional imaging studies of social rejection. *Sci Rep*., 3, 20-27.

Canaipa, R., Treister, R., Moreira, J., & Castro-Caldas, A. *Feeling hurt: pain sensitivity is correlated with and modulated by social rejection* (submetido).

Craig, AD. (2009). How do you feel-now? The anterior insula and human awareness. *Nat Rev Neurosci, 10*, 59-70.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., & Kelley, K.W., (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci. 9*, 46–56.

DeWall, C.N., & Baumeister, R.F. (2006). Alone but feeling no pain: Effects of social exclusion on physical pain tolerance and pain threshold, affective forecasting, and interpersonal empathy. *J Pers Soc Psychol, 91*, 1-15.

Dickerson, S.S., & Kemeny, M.E. (2004). Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol. Bull. 130*, 355–391.

Eisenberger, N.I., & Lieberman, M.D. (2004). Why rejection hurts: a common neural alarm system for physical and social pain. *Trends in Cognitive Science, 8*, 294-300.

Eisenberger, N.I., Jarcho, J.M., Lieberman, M.D., & Naliboff, B.D. (2006). An experimental study of shared sensitivity to physical pain and social rejection. *Pain, 126*, 132-138.

Eisenberger, N.I., Lieberman, M.D., & Williams, K.D. (2003). Does rejection hurt? An fMRI study of social exclusion. *Science, 302*, 290-292.

Gruenewald, T.L., Kemeny, M.E., Aziz, N., & Fahey, J.L. (2004). Acute threat to the social self: shame, social self-esteem, and cortisol activity. *Psychosom. Med. 66,* 915–924.

Iannetti, G.D., & Mouraux, A. (2011) Can the functional MRI responses to physical pain really tell us why social rejection 'hurts'? *Proc. Natl. Acad. Sci. U.S.A.* 108, E343.

Jørum E. (1988). Analgesia or hyperalgesia following stress correlates with emotional behavior in rats. *Pain, 32*, 341-8.

Kelly**,** M., McDonald, S., & Rushby, J. (2012). All alone with sweaty palms--physiological arousal and ostracism. *Int J Psychophysiol, 83*, 309-14.

Kendler, K.S., Hettema, J.M., Butera, F., Gardner, C.O., & Prescott, C.A. (2003). Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. *Arch. Gen. Psychiatry, 60*, 789–796.

Kross, E., Berman, M.G., Mischel, W., Smith, E.E., & Wager, T.D. (2011). Social rejection shares somatosensory representations with physical pain. *Proc. Natl Acad. Sci, 108*, 6270–6275.

Macdonald, G., & Leary, M.R. (2005) Why does social exclusion hurt? The relationship between social and physical pain. *Psychol. Bull, 131*, 202–223

Mikulincer, M., & Florian, V. (1998). The relationship between adult attachment styles and emotional and cognitive reactions to stressful events. In J. Simpson & S. Rholes (Eds.), *Attachment theory and close relationships* (pp. 143–165). New York: Guilford Press.

Monroe, S.M., Rohde, P., Seeley, J.R., & Lewinsohn, P.M. (1999). Life events and depression in adolescence: relationship loss as a prospective risk factor for first onset of major depressive disorder. *J. Abnorm. Psychol, 108*, 606–614.

Panksepp, J. (1998). *Affective Neuroscience: The Foundations of Human and Animal Emotions*. Oxford University Press

Porro, C.A. (2003). Functional imaging and pain: behavior, perception, and modulation. *Neuroscientist 9*, 354–369.

Racine M., Tousignant-Laflamme, Y., Kloda, L.A., Dion, D., Dupuis, G., & Choinière, M. (2012). A systematic literature review of 10 years of research on sex/gender and pain perception - part 2: do biopsychosocial factors alter pain sensitivity differently in women and men? *Pain, 153,* 619-35.

Tracey, I., & Mantyh, P.W. (2007). The cerebral signature for pain perception and its modulation. *Neuron, 55*, 377–39

Tracey, I., & Bushnell, M.C. (2009). How neuroimaging studies have challenged us to rethink: is chronic pain a disease? *J. Pain, 10*, 1113-1120.

Vidal C., & Jacob, J. (1986). Hyperalgesia induced by emotional stress in the rat: an experimental animal model of human anxiogenic hyperalgesia. *Ann N Y Acad Sci., 467,* 73-81.

Way, B.M., Taylor S.E., & Eisenberger, N.I. (2009). Variation in the mu-opioid receptor gene (*OPRM1*) is associated with dispositional and neural sensitivity to social rejection. *Proc. Natl. Acad. Sci. U.S.A. 106,* 15079–15084

Wiech K., & Tracey, I. (2009). The influence of negative emotions on pain: behavioral effects and neural mechanisms. *Neuroimage, 47*, 987-94.

Williams, K.D., Cheung, C.K.T., & Choi, W. (2000). Cyberostracism: Effects of Being Ignored Over the Internet. *Journal of Personality and Social Psychology, 79*, 748-762.

Woolf, C., & Salter, M. (2000). Neuronal plasticity: Increasing the gain in pain. *Science, 288*, 1765-1768.

Yoshino, A., Okamoto, Y., Onoda, K., Yoshimura, S., Kunisato, Y., Demoto, Y., Okada, G., & Yamawaki, S. (2010). Sadness enhances the experience of pain via neural activation in the anterior cingulate cortex and amygdala: an fMRI study. *Neuroimage, 50*, 1194-1201.

Canaipa, R., Fernandes, S. e Castro-Caldas, A. (2008). The Impact of Social Pain on Personal Identity, *Inter-disciplinary net*, available on http://www.inter-disciplinary.net/probing-the-boundaries/health/research-streams/health/project-archives-2/7th/session-3-pain-and-identity/

THE IMPACT OF SOCIAL PAIN ON PERSONAL IDENTITY

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Introduction

Recent research has shown that similar patterns of neuronal activation occur when someone suffers either physical pain or social rejection[1]. These patterns work as a "common alarm system", a warning to the individual about physical and social threats. This finding has given rise to the concept of social pain, in order to capture the distressing experience the individual suffers when social bonds are threatened, injured or lost[2] and to point out its resemblance to physical pain, i.e. to the unpleasant sensory and emotional experience associated with body damage or described in terms of such damage[3].

In the fields of Philosophy and Health Psychology, the concept of Social Pain encouraged the debate on the relationship between the two kinds of pain, and on its impact upon the creation and development of personal identity. By Personal Identity, we mean what defines each human being, makes him unique and different from all other human beings. Based on the contemporary philosophy of Paul Ricoeur, we also sustain that personal identity is dynamic, relational and has a narrative dimension, given that it is based on life itself and shares its temporal form[4, 5]. That is why it is important to articulate, our experiences (even the most difficult), in an intelligible plot, so that we can understand them, claim them as our own and merge them into our identity.

Both physical and social pain experiences might constitute great challenges for personal identity. We decided, therefore, to study the narratives produced by a group of patients with Fibromyalgia, a chronic pain syndrome. It has recently been argued that there may be pain processing abnormalities in those patients, which may explain why they complain of physical pain in the absence of any observable organic lesion or inflammatory process[6]. Interestingly, it is also well documented that, in parallel to the physical pain complains, one often finds a personal history of numerous traumatic life events and psychological suffering (depression and anxiety)[7]. For that reason, we decided to analyze Fibromyalgia patients, as there seems to be an interesting interrelation between physical and social pain in their lives.

Most of the studies that use qualitative or narrative research methods to understand the experiences of the Fibromyalgia patients focus on the impact of physical pain, and the meaning patients give to symptoms[8] or to the diagnostic label[9]. In spite of the importance attributed to psychological suffering in the development and maintenance of Fibromyalgia, of which the loss of significant relations would be a good example, we have not found any study employing a narrative approach and trying to understand these experiences of social pain from the patient's point of view.

The aim of this paper is to understand the impact of social pain on personal identity in a population with chronic physical pain and to clarify how individuals' experiences of extreme emotional fragility challenge their self-conceptions and self-narratives. We developed an empirical work on some of the philosophical questions that all human beings ask at certain moments of their lives: how is it possible to construct an identify for oneself, and for such an identity to persist in adversity, even in moments of extreme vulnerability? How can one live after losing the most important references of one's life's narrative, when personal identity's essential bonds vanish? How does the human being deal with grief, and social pain?

Method

Participants

We interviewed 10 women diagnosed with Fibromyalgia according to the American College of Rheumatology criteria[10]. The women were aged between 43 and 59 years. Most of the women had been dealing with the syndrome, and the physical pain it involves, for more than 3 years. They were married, with the exception of one who was single. In terms of academic achievement, there was a large variability, as we interviewed patients with only 4 years of schooling, while others that had a doctoral degree. The majority (8 cases) of the interviewed women were retired, receiving a disease compensation or were unemployed because of the Fibromyalgia. Also, in most of cases (8), women had other diseases, mainly other rheumatic diseases.

Procedure

Interview

The data was collected in Myos, the Portuguese Association for Fibromyalgia and Chronic Fatigue Syndrome, in Lisbon. Written informed consent was obtained. With our research questions in mind, we developed a semi-structured interview composed of seven open questions we thought would allow the participants to narrate their social pain experiences. In general terms, we invited the women to talk about their most significant experiences of loss or threat in relationships, the impact that those events had had in their lives and their sense of being, how they have dealt with those events and what other life events (positive or negative) were relevant to their identity., We also asked whether they thought the events of loss or threat in relationships had had any relation with the unset or persistence of Fibromyalgia. Lastly, we asked them to describe themselves, to tell us whether they felt accepted by the others and whether the interview was a painful experience. The shortest interview took only 7 minutes, while the longest went on for 90 minutes. We believe very short interviews may reflect difficulties in narrative construction, perhaps together with a failure to reflect about painful experiences. The interviews were recorded and integrally transcribed, for subsequent analysis.

Data analysis

In this study we use a Narrative Approach and choose Reissman´s narrative analysis guidelines[11]. More specifically, we analyzed the content and structure of the

patient's narrative matrix. Based on those guidelines, we developed categories of analysis for each level, which we believe can reveal a lot about the most important themes and features of the women's narratives about social pain experiences.

Narrative's Content

The narrative's content refers to the narrative production of each individual. In our study, we chose to categorize the aspects we though significant in the women's experience of social pain. We looked for the meanings women attributed to the events and their impact and then for similarities and particularities in the sample narratives. We considered as the following to be the most important themes for analysis: Social pain event; Meaning attributed to the event and Impact on personal identity. We analyzed impact in terms of emotional, relational, and personal attributes, body (Fibromyalgia), other events and self-recognizing aspects. The variety of Protagonists presented in the narrative, as proposed by McAdams[12], was also analyzed, as was the Disruption and Configuration process.

Narrative's Structure

With regard to this aspect, we claim that one important feature of the narratives is their cohesion, organization of their different aspects have and how they are integrated and sequenced as whole. We analyzed this dimension in terms of Integration, Sequence, Cohesion and Openness.

Results

Content Analysis

Types of events

Data from the interviews showed that the majority of narratives of social pain told about cases arising from kin relationships, in particular from the death of close family members (parents and brothers). Some others reported on breakups of emotionally significant relationships (e.g., divorce, offspring leaving home to live on their own).

Meaning of the events

We noticed that some of those interviewed reported several significant loss events in their lives, occurring in a short time. We examined the meaning they gave to their most significant experiences of loss, and we found that events survive the passage of chronological time, as they are perpetuated in memory; for as long as the individual will live, those events will be forgotten, they scar the person for life ("it will always be stamped on my mind ...").

As it is argued by the social pain theorists[2], those interviewed also used several expressions of physical pain to describe their social pain experiences: ("The death of my mother was as if someone had pulled out my arms", "An indelible mark, like a wound!", "I was suffocating!"). On the other hand, all meanings given were extreme and profoundly negative ("It was bad, bad, really bad"; "Loss is the worst thing that can happen").

Impact on Personal Identity

1. <u>On the emotional level</u>

At first, social pain events caused intense negative emotions on individuals. Sadness was common to all those interviewed, but these emotions also gave rise to emotional associations based on personal traits, life context and on the way events were integrated, leading to feelings of guilt, regret, anger or even despair.

As far as feelings of guilt and regret are concerned, we think they may increase social pain. Later, and with long-lasting effects, social pain caused a change in predominant mood for all those interviewed: some felt their already predominantly negative moods worsened ("I became even more sad"), while others, who had been emotionality positive in the past, changed into emotionally negative persons.

Social pain's intensity reflects the strength of the bond and the depth of the emotional relationship. However, the experience and duration of a life shared with the missing person can also strengthen the relationship bonds even between very different people. This means that, in some cases, conversation and, the sharing of ideas is not that important in strengthening a relationship; the power of a life together, the other's permanent presence and the individual's ability to accept the other as he or she is, even recognizing his or her limitations, can be enough to establish and maintain a close bond for the entire life. (My mother was "deaf and [...] belonged to another generation", but ....). Restraint of emotional expression can also impair the overcoming of social pain ("I did not cry and it was very difficult").

2. On the relational level

Initially, several participants reported needing isolation. Some became aggressive, which impaired their relationships for a while; by contrast, others developed new relationships, based on the need to protect and attend to those who also suffered from social pain.

After loss events, the majority of those interviewed strengthened their social ties and/or developed new ones (e.g.,. by performing new social roles). In cases of separation (divorce), they became more fearful and anxious about getting involved in relationships. Those who felt predominantly negative emotions also self-identified and self-differentiated negatively in comparison to others (inferiority complex)

3. On personal traits

In the beginning of the event, social pain caused some changes in personal traits. One interviewed said the experience of loss enhanced her self-reflection, another reported a self-abandonment, and a disenchantment with life, which led to several suicide attempts. However, after the initial period, these persons were able to learn and develop new skills, together with the need to be closer to others (e.g, being more useful). They also recognized that social pain had helped them become more mature and learn the importance of learning with and by suffering.

4. On the body

Considering the body, as a whole, some of those interviewed pointed out that it reacts to emotions. Greater nervousness, headaches, growing fat, and even an inability to walk were some of the body effects caused by social pain. In addition, although our participants did not link social pain to Fibromyalgia, some noted a worsening of Fibromyalgia symptoms following events, and recognized that stress and the restraint of emotions may cause more pain.

5. Other events

When asked to narrate other important events in their lives that they considered to have had an impact on personal identity, those interviewed mainly reported and valued negative events (feelings of loss, disease, relational conflicts). For many, the Fibromyalgia syndrome acted as a 'turning point' in their lives, in at least two ways. On one hand, the syndrome was a negative experience, because it brought many constraints: pain, loss of autonomy and a feeling of being useless. One participant even said that, after the syndrome: "I was never the same". However, for others, Fibromyalgia was also felt to be a positive event, because it made them more sensitive to others, especially to the vulnerable and fragile; it also forced them to better structure their lives, focusing on what is essential and leaving the accessory aside. One participant said the syndrome made him value spiritual goods and devalue material goods'; it changed his view of life so radically, his understanding of the world and his place in it that he confessed: "I thank God, because I became a better person."

Three individuals were unable to mention any positive events in their lives. Positive

events reported were mainly connected with the establishment of new bonds, like motherhood, births, marriages and happy experiences of childhood.

6. Self-recognition

At the time of the interview, the subjects recognized themselves as the same self as in the past, in spite of the social pain they experienced and the changes they had gone trough. This means that chronological and psychological time, as well as a life's history built in relation to the other, are essential factors in self-constitution, inner balance and self-recovery.

Only one participant did not self-recognize as the same, but he was also the only one who did not report social pain events. He focused on the syndrome and on its pain effects throughout the interview.

The majority of thoe interviewed showed a unified self, especially due to strategies to surpass pain. Participants who showed an inability to overcome social pain also displayed a permanent conflict identity, especially felt in negative emotions, like regret or dilemmas between being and duty.

Disruption and Configuration

1. Self-disruption

Initially, the experience of social pain disrupts personal identity, because it causes emotional unbalance and deeply challenges self-conceptions, the personal world-view , and the meaning of a good life (life's goals, ultimate values and ideals). In fact, social pain was lived by some interviewed as an “emotional shock”, like deep sadness and despair, emotions that were so powerful they precluded any possibility of self-control and threw the individual radically out of balance. (“It was really a trauma for me”, “It was horrible”, “It was a shock”, “I felt emptiness”, " I felt unable to do anything”, “I tried to commit suicide four times”). In several cases, the experience of social pain also caused changes in personal traits, especially in mood, that remained until the time of the interview.

Finally, in some cases, social pain led to an ethical reflection about the best way to live, which had effects on the individual’s actions and personal life. For example, one participant changed his career path and another went to live in another country.

2. Self-configuration

The way from s*elf-disruption to self-configuration* is unique and particular to each person interviewed, and each one pursues it at his or her own pace. However, the way the memory of the lost tie is framed appears to be a major challenge to that process. Several of those interviewed seemed to use the available cultural discourse to understand the loss, justifying it as a 'natural law of life ". However, this effort to understand and accept the event, as a natural fact of life, appears to be unsatisfactory for them

The awareness that life is a gift and the experience of chronological time (“the passing of years") allows the self-resettlement (the overcoming of pain without losing its memory). On the other hand, caring for others and the ability to create new emotional bonds appear to be essential to self-configuration

On the contrary, women who used “escape strategies” seem to have had more difficulty in self-configuration. Finally, the lack of affective ties is the main obstacle to overcoming the loss and constructing a new self-configuration. “[...] if I had a backup, perhaps I would have already made something of my life".

Protagonist

Participants narrated their stories of loss, identifying themselves with the following *Imago types*[11]*: the survivor, the caregiver, the maker* and *the sage*. Women's narratives who were, above all, of *survivors* seem to indicate stagnation and

difficulty of rebuilding through action, relationships and understanding the impact of painful events on their identity.

Structure

Integration

The sequence of the narrative depended on the order of the semi-structured interview issues. Narratives were not always organized according to linear time and there were frequent forward and backward movements. We were, however, able to identify three levels of narrative.

1. Disintegrated

   A plot composed using only with short story fragments and ideas. We identified three narratives of this type.

2. Descriptive

   Narratives developed from descriptions of actions and behaviors, without any systematic reflection on these situations and their impact on personal identity. Four cases constructed their narratives in these terms.

3. Explanatory

   Integrated narrative, where the description of events is complemented with the assignment of meanings to those events and with (some) reflection about their impact on personal identity. Three women were able to integrate their experiences of social pain in this form.

Emotional Tone

As far as emotionality is concerned, we identified three sorts of narrative

1. Negative focus

   Narratives that are focused on negative events, negative meanings and negative emotions, like sadness and anger

2. Turning negative into positive path

   Similar to narratives of "redemption", the life story sequence begins with the description of loss events and social pain, and leads to positive events and positive emotions[11]

3. Balance between positive and negative emotions

   Narrative sequences in which, after negative events and meaning, positive meanings and emotions are immediately ascribed to that same event. These narratives illustrate the personal effort of instantaneously turning to positive all negative events.

Consistency

Most narratives reveal inconsistencies, omissions and inaccuracies. Some participants were unable to create and develop a narrative about themselves and their lives, and, when they did, it was always constructed in a superficial way. Data show how difficult it is to become, at the same time, the subject and the object of knowledge.

Despite considering the events of loss as meaningful, the interviewees did not seem prepared to reflect, in a narrative way, on that loss, especially with regard to three factors: a) they more often narrate the emotional bond with the lost person, than the event itself and its impact on their identity; b) reflexion on effects upon personal identity is neglected over description of everyday life; when it is done, it is usually vague and superficial; c) finally, the participants' descriptions of actions sometimes do not fit with the behavior they saw as helpful in overcoming social pain.

Openness

Most interviewees showed difficulty in reflecting more deeply on the impact of loss on identity, rendering difficult the openness required for the creation of new meanings. We can therefore sustain that the main phase of opening up to new meanings occurs at the moment of disruption, because after the meanings are assigned, individuals tend to become more rigid and less vulnerable to change.

In some interviews, the act of narrating improves the understanding of events and helps to overcome pain ("It makes me feel good to talk to my father about my brother", "It is very difficult, [but] it brings relief").

Conclusions

All the previous stories of loss are stories of the pain that love can bring about: a love with a strong emotional dimension, which is focused on the "desire to live together", on the need to create a common and "shared history"[13]. Hence, human love is permanently under threat, for it can be disrupted by separation or actual loss. That is why the narrated events – the loss of significant relationships (social pain) - were considered the most meaningful events of their lives. Loss is "the worst thing that can happen".

The problem of death, the awareness of the temporary and finite side of life, remains the main problem for the majority of those interviewed. The issue of death is evaluated not in the first person, but by putting the problem of how to live after the departure of others with whom we shared our lives and whom we loved deeply

The way to maintain a meaning for life and a personal identity, after its disruption by social pain, rests on the individuals' ability to identify with their past, with the memories of their social and affective bonds, with their actions and interactions carried out after the event. Social pain is overcome through the establishment of new affective and social bonds, which also promote new ways of being (new roles) and self-esteem. Hence, identities without affective ties showed more difficulty in overcoming the loss and reconstructing their lives. Human beings can live without love, but not live well. Self-configuration is also hampered in someone who lives with internal conflicts or encloses emotions.

Integrated (explanatory) narratives match with structured identities (identities able to unify the different parts of lives) and are better in helping to overcome pain, although the majority of those interviewed showed difficulty in building self-narratives, describing almost only events of social pain and their impact on personal identity.

For some women, we notice that Fibromyalgia and the pain that it involves may disrupt the personal identity even more than the social pain. In these cases the syndrome is felt to be a "turning point" in their lives. Although models that try to explain the onset and maintenance of Fibromyalgia highlight the important role of chronic stress and traumatic experiences in the syndrome, most of those we interviewed showed a dualist mind-body perspective. Most did not identify any kind of influence of social pain on physical pain.

There is also a correlation between pain experience in the act of narration, focus on negative emotions and difficulty in self-reflexion. Finally, in most cases, we notice that personal identity may be strongly determined by negative events that have been happening during life.

References

1. N. Eisenberger, M. Lieberman & K. Williams, 'Does rejection hurt? An fMRI study of social exclusion'. *Science,* vol.302, 2003, pp. 290-292.
2. N. Einsenberger & M. Lieberman, 'Why rejection hurts: a common neural alarm system for physical and social pain'. *TRENDS in Cognitive Sciences, 8*, 7, 2004, pp.

294-300.
3. IASP. '*Classification of chronic pain: descriptors of chronic pain syndromes and definitions of pain terms*'. Seatle, IASP Press, 1994.
4. P. Ricoeur, '*Soi-même comme un autre*'. Paris, Éditions du Seuil, 1990.
5. P. Ricoeur, '*Philosophie de la* Volonté' *I,*Aubier, Paris, 1988.
6. R. Staud, 'Biology and therapy of fibromyalgia: pain in fibromyalgia syndrome'. *Arthritis Research and Therapy, 8*, 2006.
7. J. McBeth, G. Macfarlane, S. Benjamim, S. Morris, & A. Silman, 'The association between tender points, psychological distress, and adverse childhood experiences: a community-based study'. *Arthritis and Rheumatism*, vol. 42, 1999, pp. 1397-1404.
8. S. Söderberg, B. Lundman & A. Norberg, 'The meaning of fatigue and tiredness as narrated by women with fibromyalgia and healthy women'. *Journal of Clinical Nursing, 11*, 2002, pp. 247-255.
9. S. Madden & J. Sim, 'Creating meaning in fibromyalgia syndrome'. *Social Science & Medicine, 63*, 2006, pp. 2962-2973.
10. F. Wolfe, H. A. Smythe, M. B. Yunus, et al., 'The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: Report of the Multicenter Criteria Committee'. *Arthritis and Rheumatism, 33*, 2, 1990, pp. 160-172.
11. C. Reissman, '*Narrative Analysis'*, Sage, London, 1993.
12. D. P. McAdams, '*The Person: A New Introduction to Personality Psychology*'. New York, Wiley, 2000.
13. M. Nussbaum, '*The Fragility of Goodness*'. Cambridge, Cambridge University Press, 2001.

3. POSTERS/ABSTRACTS

Canaipa, R., Moreira, J. M. & Castro-Caldas, A. (2013). Feeling Hurt: Social Rejection Modulates Sensory Dimensions Of Physical Pain, *8th "Pain in Europe" European Federation of International Association for the Study of Pain Chapters Congress*, EFIC, Florence, Italy.

Background and aims: It is assumed that social pain, resulting from injury of social bonds, may have co-opted the neuroanatomical bases of the emotional aspects of pain experience (Eisenberger et al., 2003). A recent paper, however, has shown that social pain may also involve the sensory areas (Kross et al., 2011). Therefore, the current study, employing electrical stimuli, aims to investigate whether a social pain manipulation shows impact on sensory dimensions of physical pain and to understand the impact of psychological characteristics on susceptibility to pain.

Methods: 33 healthy participants answered questionnaires measuring a number of physical and psychological characteristics. After obtaining their electrical pain threshold (in terms of intensity of pain) participants played Cyberball, a virtual ball tossing game designed to manipulate social rejection feelings. After this manipulation, they were exposed to painful stimuli, and rated their intensity and unpleasantness. It was hypothesized that rejected participants would rate stimuli as more intense and more unpleasant.

Results: Rejected individuals felt greater pain intensity when compared to non-included and included participants. This effect was mediated by low control perceptions in the Cyberball situation. Pain was correlated with perceived life stress and low feelings of personal efficacy.

Conclusions: Social rejection changes intensity ratings of physical pain derived from rapid nerve fibers. This effect lasts after the rejection situation and is apparently mediated by feelings of low control and efficacy in social situations. These results show that social rejection may impact on sensory, and not only emotional, dimensions of physical pain.

Canaipa, R. e Castro Caldas, A. (2009). A dor na Fibromialgia: uma revisão crítica dos estudos que utilizam neuroimagem, *XVII Jornadas Internacionais do Instituto Português de Reumatologia* (Abstract in *Acta Reumatológica Portuguesa, 34*, nº4B, Out/Dez de 2009.)

As Neurociências têm contribuído significativamente para a compreensão e estudo da dor. O desenvolvimento e crescente utilização de técnicas de neuroimagem têm revelado dados importantes sobre os mecanismos de processamento neural da dor, em indivíduos saudáveis, e as alterações que ocorrem nesses mecanismos, em várias doenças e síndromes de dor crónica.

A presente revisão da literatura tem como objectivo reorganizar e analisar criticamente os resultados das investigações que utilizam técnicas de neuroimagem na clarificação do processamento da dor na Fibromialgia e reflectir sobre as implicações destes estudos para a concepção desta síndrome, enquanto entidade clínica relevante, que envolve dimensões físicas e emocionais, e enquanto perturbação do processamento da dor.

Têm sido verificadas alterações estruturais, funcionais e neuroquímicas no cérebro dos indivíduos com Fibromialgia. Os resultados destes estudos sugerem a existência de uma disfunção na resposta neuronal à dor, caracterizada sobretudo por um processamento que é qualitativamente similar ao dos indivíduos saudáveis, mas que é quantitativamente amplificado. Esta amplificação é coincidente com os relatos verbais de dor e não é explicada pelos níveis de depressão dos pacientes.

Não obstante, alguns dos estudos aqui revistos apresentam algumas limitações, nomeadamente, no que diz respeito aos grupos de comparação utilizados, o que condiciona a distinção entre o que constituem os mecanismos disfuncionais do processamento da dor que são comuns a todas as síndromes que envolvem dor crónica, e os mecanismos que poderão ser específicos à Fibromialgia.

Canaipa, R., Moreira, J., (2009). "Credibility issues as barriers to the construction of happiness of persons with medically unexplained diseases", *16th Congress of the European Association for Psychotherapy "Meanings of happiness and psychotherapy"*, Lisboa.

Psychotherapy in chronic diseases frequently involves a redefinition of the patient's life goals and personal identity, and also the construction of a new meaning for happiness. Although psychotherapy usually concentrates on overcoming physical limitations and psychological suffering, less attention is devoted to subtle barriers involving credibility and interpersonal matters. In diseases where medical explanation is incomplete or absent, like the Fibromyalgia syndrome, these subtle barriers may be highly relevant to achieve psychotherapeutic goals. In spite of advances in the comprehension of abnormal pain processing mechanisms, hormonal production and sleep patterns in Fibromyalgia, the syndrome is still discredited by some health professionals and patients' relatives, and treated as something occurring "just in the patients' heads".

In psychotherapeutic interventions with this specific population, the goal of meaning and happiness is frequently overwhelmed by these credibility aspects, and the patient may strive for a sick role incongruent with adaptation and recovery from pain and social loss. We will discuss some aspects relevant for interventions in this syndrome. We believe that it is futile to develop interventions designed to help construct new meanings for life and self-fulfillment goals if the patients fear that such enhancement will be interpreted by others as evidence for a psychosomatic cause or lack of credibility for the syndrome.

Moreover, it is also difficult for these patients to construct meaning from an experience that not only causes pain and marked physical limitations, but also disrupts personal relationships and trust in others. Psychotherapeutic interventions should (a) target not only physical but also the equally relevant social pain, (b) consciously address the "credibility vs happiness dilemma" and (c) help construct bridges between the patient and significant others, where the disease may be well understood, therefore allowing for the construction of new meaning and happiness from these complex physical and social pain experiences.

Canaipa, R. e Moreira, J. M. (2008). Perfil de personalidade em pacientes com Fibromialgia seguidos na consulta de psicologia da Myos. *XVI Jornadas Internacionais do Instituto Português de Reumatologia*, Abstract in *Jornal do Instituto Português de Reumatologia*, vol 7, nº1, Out/Dez de 2008.)

Introdução: O objectivo deste trabalho foi o de identificar os padrões, mais ou menos disfuncionais, de funcionamento psicológico habitual que se desenvolvem perante a vivência com a síndrome fibromiálgica. Não se pretende definir um perfil de personalidade associado a esta síndrome, um objectivo que estudos anteriores já demonstraram não ser viável, mas sim caracterizar formas típicas de lidar com a doença e suas implicações pessoais, interpessoais e sociais, com possíveis implicações para a sua evolução, e cujo conhecimento poderá ser útil aos profissionais de saúde e aos próprios pacientes na gestão da doença

Método: Este trabalho foi realizado com 33 mulheres com Fibromialgia que foram seguidas na consulta de Psicologia, de orientação cognitivo-comportamental, na Myos, Associação Nacional contra a Fibromialgia e Síndrome de Fadiga Crónica. Foi utilizado um questionário de avaliação da personalidade em contexto clínico, o Inventário Clínico Multiaxial de Millon-II.

Resultados: Os resultados devem ser interpretados com precaução, uma vez que não existe grupo de controlo e se trata de um questionário que não foi até ao momento adaptado para a população Portuguesa. Contudo, acreditamos que, pelas suas excelentes qualidades psicométricas de origem, uma leitura cuidada e conservadora dos seus resultados nos pode apontar pistas interessantes para a compreensão das dimensões de personalidade nesta afecção. Verificámos um ligeiro aumento em duas escalas de personalidade, de severidade moderada, as escalas Evitante e Autodestrutiva, e em duas escalas de sintomatologia, de severidade moderada, Ansiedade e Depressão. Não verificámos aumentos significativos em escalas indicadoras de perturbação severa, o que é importante, sobretudo se tivermos em conta que se trata de uma população clínica.

Mais ainda, foi possível verificar que (a) foram as pacientes que recorreram à consulta com o intuito de realizar avaliação para junta médica de verificação de incapacidade profissional, (b) as que não se encontram profissionalmente activas que se revelaram mais perturbadas; e ainda (c) que o intervalo de tempo decorrido desde o diagnóstico de Fibromialgia parece estar associado a diferenças nas escalas de personalidade, no sentido de uma patologia mais severa.

Conclusão: Estes resultados parecem contrariar a perspectiva de que os pacientes com Fibromialgia são, por características individuais, mais propensos a perturbações de personalidade severas e sugerem que as formas habituais de funcionamento destes pacientes reflectem a importância da vivência com uma sintomatologia dolorosa difusa, imprevisível e incapacitante, no desenvolvimento de perturbação psicológica. A compreensão destes padrões pode permitir uma melhor gestão desta síndrome pelos pacientes e pelos profissionais de saúde que intervêm no seu tratamento.